PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

ADVISORY COMMITTEE BRIEFING DOCUMENT

BLA 103948

Advisory Committee Meeting

November 13, 2013

Genzyme
500 Kendall Street
Cambridge, MA 02139

AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ANC	absolute neutrophil count
ARR	annualized relapse rate
AUC	area under the concentration-time curve
B-CLL	B-cell chronic lymphocytic leukemia
BPF	brain parenchymal fraction
CBC	complete blood counts
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CRO	contract research organization
CTC	common toxicity criteria
DMT	disease-modifying therapy
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
GBM	glomerular basement membrane
HLT	high level term (MedDRA)
HPV	human papillomavirus
HR	hazard ratio
IAR	infusion-associated reaction
IC_{50}	half maximal inhibitory concentration
IFNB-1a	interferon beta-1a
ITP	immune thrombocytopenia purpura
IV	intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NOAEL	no-observed-adverse-effect level

PD	pharmacodynamics
PML	progressive multifocal leukoencephalopathy
PK	pharmacokinetics
PT	preferred term (MedDRA)
RAP	relapse adjudication panel
REMS	Risk Evaluation and Mitigation Strategy
RRMS	relapsing-remitting multiple sclerosis
SAD	sustained accumulation of disability
SAE	serious adverse event
SC	subcutaneous
SOC	system organ class (MedDRA)
SPMS	secondary progressive multiple sclerosis
SRD	sustained reduction in disability
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1. Executive Summary

Alemtuzumab is an intravenously infused humanized monoclonal antibody which targets CD52, which is expressed at high levels on B and T lymphocytes. Originally developed for the treatment of B-cell lymphocytic leukemia (B-CLL), pilot studies in multiple sclerosis (MS) patients using a dosing regimen different from that in oncology, suggested a substantial effect on relapses and disability progression. As a result, the Sponsor conducted 3 efficacy and safety studies of alemtuzumab versus an active comparator to evaluate its potential to slow the accumulation of physical disability and reduce the frequency of clinical exacerbations in patients with relapsing-remitting MS. The findings from these studies were submitted to FDA in November 2012 as a supplemental Biologics License Application (sBLA). The results of the three studies demonstrating strong efficacy in relapsing MS patients, coupled with a well-characterized and manageable safety profile, support a favorable benefit-risk assessment and approval of this sBLA for MS. This document summarizes the continuing unmet medical needs in patients with MS, the rationale for using alemtuzumab to address these needs, the efficacy and safety information supporting use of alemtuzumab, and the overall benefit-risk assessment derived from a clinical program that includes nearly 1,500 MS patients treated with alemtuzumab.

1.1 MS Background

MS is a chronic disorder of the central nervous system (CNS), involving damage to brain, spinal cord and optic nerves. MS represents the leading cause of neurologic disability in young and middle-aged adults, affecting approximately 400,000 people in the United States (National Multiple Sclerosis Society, 2011). MS is more common among women than men and affects people in the prime of life with most people diagnosed between the ages of 20 and 50 years. The etiology of MS is unknown but is thought to involve both genetic and environmental components. Inflammatory infiltrates consisting of lymphocytes (T cells and B cells) and activated macrophages/microglia damage the CNS are the most prominent factor underlying the pathogenesis of MS (Lassmann, 1998, *Mult Scler*; Compston, 2008, *Lancet*).

It is estimated that as many as 80% of all MS patients present with relapsing remitting MS (RRMS) (Noseworthy, 2000, *N Engl J Med*). The clinical course of RRMS typically manifests as initial episodes of transient neurological compromise (also called relapses or clinical exacerbations) with variable periods of recovery (remissions). Common relapse symptoms include paresis (weakness) and incoordination, and impairments in gait, sensation and vision, loss of bladder and bowel control, and sexual dysfunction. Relapses differ in severity and a

patient may or may not fully recover from each episode. Eventually, such relapses lead to cumulative deficits that may increase acutely with each new exacerbation and result in accrued physical disability.

MS relapses are caused by focal inflammatory lesions causing demyelination and axonal transection, which interrupt neuronal signaling and lead to the symptoms of MS. But clinically evident relapses are just the "tip of the iceberg" in terms of MS-related injury to the CNS. Inflammatory damage below the threshold of clinical detection occurs even during periods of apparent remission (Frischer, 2009, *Brain*; Kuhlmann, 2002, *Brain*; Lucchinetti, 2011, *N Engl J Med*) and gradually erode the brain's compensatory reserve and contribute to brain atrophy and long-term disability risk.

MS-related disability has a profound and lasting impact on the way a patient feels and functions, often limiting their vision, cognition, muscle strength and coordination and their ability to ambulate. In natural history studies, one-third of people with MS become unable to walk, and many more will need an aid such as a cane or walker or scooter. The psychological and social consequences from such disabilities are significant as patients often suffer from depression, rely heavily on family and other care givers for assistance and give up meaningful employment due to physical and cognitive limitations.

Over time, approximately 70% of patients with relapsing forms of MS develop secondary progressive MS (SPMS), characterized by deterioration that steadily worsens over time with or without periodic relapses or remissions, leading to permanent disability. Available MS therapeutics are largely ineffective in slowing deterioration for patients with SPMS as reflected by the fact that almost none are indicated as treatments for patients with progressive MS.

Thus, early therapeutic intervention to suppress CNS inflammation is important to prevent MS relapses, to reduce subclinical injury, and thereby to slow the accumulation of disability and consequent risk of SPMS.

1.2 Unmet Medical Need in Patients With MS

Currently, there are several marketed products shown to have MS disease-modifying effects, as described in Section 2.1.1. Efficacy varies among currently approved disease modifying therapies (DMTs) and most patients who receive these treatments continue to experience "breakthrough" disease activity (relapses and new brain lesions) and continued disease progression which are prognostic indicators for poor long-term outcomes. Breakthrough disease activity indicates ongoing inflammation and accumulation of tissue damage even when it

remains clinically silent. It is common to initiate treatment with a DMT having modest efficacy but also a comparatively low risk of serious complications. Patients who have inadequate response to initial therapy (i.e., breakthrough activity) may be switched to another therapy, often another "platform" DMT delaying treatments with higher efficacy but increased risk.

Delaying initiation of highly effective therapy in patients with early, active disease may come at the cost of irreparable axonal loss and scarring of brain and spinal tissue. With increasing evidence of long-term consequences of inadequate disease suppression, many MS experts are opting to initiate treatment with a more highly effective therapy in order to prevent severe, disabling relapses, continued lesion formation and, ultimately, permanent accrual of disability. This shift in thinking on the part of physicians highlights two important unmet needs in the treatment of patients with relapsing forms of MS that the development program for alemtuzumab was designed to address:

- The need of treatment-naïve patients for a treatment that will more effectively reduce both the likelihood of relapse and the risk of disability, thus reducing the risk of breakthrough disease activity and resultant progression of irreversible disability;
- The need of patients experiencing breakthrough disease activity while using DMT for a treatment shown to more effectively reduce both the likelihood of relapse and the risk of disability. For such patients with breakthrough activity, there has been little controlled data to guide subsequent treatment decisions.

Since no approved DMT regimen has been shown to reduce relapses or to slow disability progression more effectively than any other, a treatment proven to be more effective than the most effective platform therapy would represent an advance towards meeting these needs, and an important addition to the existing range of treatment options for patients with RRMS.

1.3 Rationale for Investigation of Alemtuzumab in MS

Lymphocyte-mediated inflammation in the CNS is the most prominent factor underlying the pathogenesis and clinical manifestations of RRMS (Compston, 2008, *Lancet*) Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen present at high levels on the surface of T and B lymphocytes, leading to their depletion. While the exact mechanism responsible for alemtuzumab's effects on MS disease activity is not clearly defined, the depletion and repopulation of lymphocyte subsets observed following administration is hypothesized to modulate the immune system and likely contribute to the observed therapeutic effect.

Alemtuzumab development for treatment of MS began with open-label, investigator-sponsored studies. A pilot study conducted in patients with SPMS found that alemtuzumab significantly decreased annualized relapse rates and formation of new lesions in the CNS (Moreau, 1996, *Mult Scler*). In a study conducted in patients with RRMS, alemtuzumab produced sustained reductions in disability scores, an effect not observed in patients with SPMS, as well as sustained reductions in relapse rates and lesion formation (Coles, 2006, *J Neurol*). These studies provided the impetus for Genzyme's clinical program in the RRMS patient population.

1.4 Clinical Development Program

The investigator-sponsored, pilot studies in MS informed the design of a Genzyme-sponsored, randomized, rater-blinded, active-controlled Phase 2 trial (CAMMS223) of patients with RRMS who were naïve to any prior DMT. Unlike other Phase 2 trials in MS which focused on short-term MRI outcomes in placebo controlled studies, Genzyme's Phase 2 study evaluated primary endpoints of relapse and disability in a comparison between alemtuzumab and Rebif® (subcutaneous interferon beta-1; SC IFNB-1a) over 3 years of follow-up. Results of the Phase 2 study affirmed alemtuzumab's potential as a treatment for MS. Two Phase 3 trials were conducted: one in treatment-naïve patients (CAMMS323) and one in patients who had experienced disease activity on another DMT (CAMMS324) as evidenced by at least 1 relapse during prior treatment (for ≥ 6 months) with beta interferon or glatiramer acetate.

As with the Phase 2 study, the Phase 3 studies were randomized, open-label, rater-blinded, active-controlled studies comparing the safety and efficacy of alemtuzumab to high-dose Rebif in patients with RRMS. Rebif is an approved MS treatment that decreases the frequency of MS relapses, delays the accumulation of physical disability, and reduces the development of new T2-hyperintense or enhancing brain lesions on MRI. Compared with a placebo-controlled design, the active-comparator design versus Rebif set a high hurdle for demonstrating efficacy and a positive benefit/risk profile given that it was also recognized that alemtuzumab may have potentially serious side effects.

The Phase 3 studies had the same co-primary efficacy endpoints as the Phase 2 study: relapse rate, and time to 6-month sustained accumulation of disability (SAD) based on the Expanded Disability Status Scale (EDSS). The EDSS is the scale most often used to assess disability in clinical trials in MS (Cohen, 2012, *Lancet Neurol*). Blinded raters performed quarterly EDSS exams from which the 6-month SAD endpoint was determined, as well as another disability-related endpoint, the Multiple Sclerosis Functional Composite (MSFC). In addition, the blinded rater also performed an EDSS exam at the time of a suspected relapse. However, to preserve

study integrity, blinded raters were not permitted to access clinical data required to make the determination of what constituted a relapse. Rather, all relapse determinations were made by a blinded Relapse Adjudication Panel (RAP) comprised of 6 independent neurologists based upon their review of EDSS score and other assessments following a standardized relapse definition specified in the study protocol.

In addition to the blinded assessment of the primary and secondary clinical endpoints, all cranial MRIs were evaluated by blinded neuroradiologists at an independent central MRI facility using anonymized scans.

For both Phase 3 studies, the Hochberg method was used to control for Type I error rate and the protocol-defined criterion for study success was a statistically significant treatment effect of alemtuzumab over Rebif for either or both of the co-primary efficacy endpoints.

An ongoing extension study (CAMMS03409) enrolled eligible patients who participated in the Phase 2 and Phase 3 studies.

1.5 Regulatory History

Because of its ability to target lymphocytes, alemtuzumab was initially developed as a treatment for B-CLL and was approved for this use in the United States on 07 May 2001 under Biologics License Application (BLA) 103948.

The Sponsor undertook development of alemtuzumab in MS in 2002 via the long-term Phase 2 study CAMMS223. In 2005, 3 cases of immune thrombocytopenic purpura (ITP), including the index fatal case, were identified in 2005. This led Genzyme to suspend dosing in the Phase 2 study, consistent with the recommendation of the safety monitoring board. FDA placed a partial clinical hold on the IND which was subsequently lifted in 2007 largely due to implementation of a risk mitigation plan including monitoring for signs and symptoms of ITP as well as submission of two adequate and well-designed Phase 3 study protocols (CAMMS323 in naïve patients and CAMMS324 in patients with breakthrough disease activity).

In contrast to the approach taken in development programs for other DMTs that have included placebo-controlled studies, Genzyme chose to use an active comparator in all clinical studies of alemtuzumab in order to evaluate its effect versus a known standard of care for MS. High-dose Rebif was selected as the comparator because at the time these studies were initiated, it was considered by many to be the most effective DMT for MS, since it had an established effect on relapses and MRI lesions superior to that of Avonex as measured in an open-label, rater-blinded,

head-to-head study (Panitch, 2002, *Neurology;* Rebif US Prescribing Information), supporting its approval in the US. FDA agreed with the choice of Rebif for the active-controlled trial, but recommended a double-dummy placebo controlled design for the pivotal trials, using both sham infusions and sham injections over the course of two years. However, the choice of Rebif as a comparator posed a significant challenge to creating a true placebo-controlled design as it was only available in proprietary, pre-filled syringes that could not be masked. In addition, both alemtuzumab and Rebif had well-known side effect profiles detailed in their prescribing information that would subvert blinding efforts. As an example, during alemtuzumab IV infusions, nearly all patients experience infusion-associated reactions (Moreau, 1996, *Brain*), which often include headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnoea, generalized rash, and dizziness. With a markedly different time and mode of administration (3-times weekly self- or other-administered by SC injection), Rebif also has a distinct safety profile, with many patients experiencing injection site reactions and flu-like symptoms (Rebif US Prescribing Information, 2011). With the desire to maintain both an effective comparator arm and the study blind Genzyme chose a rater-blinded design and taking Agency concerns into consideration carefully developed the procedures necessary to ensure study integrity and interpretability of the results. These included study documents (protocol, study operations manual, monitoring manual, informed consent form, etc.) which detailed the procedures required to ensure and maintain blinding, training of site staff to ensure awareness of blinding requirements, documentation and monitoring for compliance with blinding requirements throughout the study, assessing any potential events of unblinding as well as their potential impact on results through pre-specified statistical analysis, and review of relapse and MRI imaging endpoints by independent, blinded reviewers (see Section 3.3).

1.6 Summary of Efficacy Findings

In Phase 2 Study CAMMS223, a study of alemtuzumab (12 mg/day) vs. Rebif in 334 treatment-naïve MS patients, alemtuzumab demonstrated significant effects vs. Rebif at 3 years, as demonstrated by:

- Reduction in the relapse rate by 67% for alemtuzumab 12 mg/day compared with Rebif ($p<0.0001$) over 3 years; 50% of Rebif-treated patients and 24% of alemtuzumab 12 mg/day treated patients had experienced a relapse by Year 3;
- Reduction in the risk of SAD by 76% for alemtuzumab 12 mg/day compared with Rebif ($p=0.0006$) over 3 years; 27% of Rebif-treated patients and 8% of alemtuzumab 12 mg/day-treated patients had experienced SAD by Year 3;

- Reduction (improvement) in EDSS score in those receiving alemtuzumab (-0.36) as compared with a mean increase (worsening) in Rebif-treated-patients (0.41); there was a difference between the treatment groups of 0.76 ($p<0.0001$). In addition, in patients with pre-existing disability at baseline, i.e., with an EDSS scores of at least 2.0, alemtuzumab-treated patients were 2 times more likely than Rebif treated patients to have achieved a sustained reduction in disability (SRD) as measured by at least a 1 point reduction in EDSS score sustained for 6 months, a clinically meaningful change ($p=0.0106$).

In Phase 3 Study CAMMS323, a study of alemtuzumab 12 mg/day vs. Rebif in 581 treatment-naïve patients, alemtuzumab demonstrated significant effects compared with Rebif and criteria for study success were fulfilled. A summary of these results is as follows:

- Reduction in the relapse rate by 55% compared with Rebif ($p<0.0001$) over 2 years; 39% of Rebif treated patients and 18% of alemtuzumab 12 mg/day treated patients experienced a relapse by Year 2;
- Increased percentage of alemtuzumab-treated patients who were relapse-free at Year 2 compared with Rebif ($p<0.0001$), and patients experienced fewer severe relapses ($p=0.0056$), and fewer relapses that were treated with steroids ($p<0.0001$);
- Reduction in the risk of SAD through 2 years by 30% for alemtuzumab compared with Rebif, which did not achieve statistical significance ($p=0.2173$). The percentage of patients experiencing SAD at 2 years was 8% of alemtuzumab-treated patients compared with 11% in the Rebif group.

In Phase 3 Study CAMMS324, a study of alemtuzumab 12 mg/day vs. Rebif in 840 MS patients who had experienced disease activity while on a prior therapy, alemtuzumab demonstrated significant effects compared with Rebif. A summary of these results is as follows:

- Reduction in the relapse rate by 49% compared with Rebif ($p<0.0001$) over 2 years; 52% of Rebif treated patients and 26% of alemtuzumab 12 mg/day treated patients experienced a relapse by Year 2;
- Increased percentage of patients who were relapse-free at Year 2 compared with Rebif ($p<0.0001$), and patients experienced fewer severe relapses ($p=0.0121$), and fewer relapses that were treated with steroids ($p<0.0001$;

- Reduction in the risk of SAD through 2 years by 42% for alemtuzumab as compared with Rebif that was significant (p=0.0084); the percentage of patients experiencing SAD at 2 years was 12.7% in the alemtuzumab group compared with 21.1% in the Rebif group;
- Reduction (improvement) in EDSS score in those receiving alemtuzumab (-0.17) as compared with a mean increase (worsening) in Rebif-treated patients (0.24); there was difference between the treatment groups of 0.41 (p<0.0001). Also similar to the Phase 2 study, alemtuzumab-treated patients with pre-existing disability were 2.5 times more likely to experience a sustained reduction in disability score than were Rebif treated patients (28.8% vs. 12.9%, p=0.0002).

The improvement in mean level of physical disability observed in alemtuzumab-treated patients in the Phase 2 study, and again in the Phase 3 study CAMMS324 was noteworthy as an improvement in disability score sustained for 6 months (as opposed to slowing of progression) has not been established with other approved DMTs.

Sensitivity analyses demonstrated that the primary efficacy conclusions were robust and uninfluenced by the very few instances of unblinded EDSS assessments (<1% of all assessments), missing data due to patient dropout and other factors that could potentially impact study results (Section 4.1.3). Subgroup analyses confirmed that the results were generally similar across subgroups regardless of disease activity or prior treatment history (Sections 4.1.3.6 and 4.1.4).

Importantly, effects on clinical endpoints across studies were also supported by significant effects on a range of imaging endpoints:

- A significant reduction in in the number of patients with new gadolinium enhancing lesions and new or enlarging T2-hyperintense lesions which are associated with acute inflammatory disease activity;
- A significant reduction in the number of patients with new T1-hypointense lesions which are associated with axonal injury; and
- A significant slowing in the rate of brain volume loss as determined by brain parenchymal fraction (BPF), a measure of brain atrophy.

Alemtuzumab was highly efficacious on a wide range of meaningful clinical and MRI endpoints over and above the effects of Rebif on these measures. Results were consistent across

populations with relapsing forms of MS, encompassing treatment-naïve patients with active disease as well as patients who have experienced continued clinical disease activity while on prior therapy.

1.7 Summary of Safety Findings

The clinical safety experience with alemtuzumab treatment includes 1,486 MS patients treated with alemtuzumab and >5,400 patient-years of collective follow-up. The majority of patients (1078, 72.5%) received 2 cycles of study drug; 23.3% received >2 cycles. Median duration of follow up for all alemtuzumab-treated patients was 43.2 months. A total of 1241 (83.5%) alemtuzumab-treated patients had at least 2 years of follow up and 444 (29.9%) had ≥4 years of follow-up; a small number of patients have been followed for up to 9 years.

The safety database is also informed by an analysis information from clinical trials of Campath in B-CLL where alemtuzumab was administered at higher and more frequent doses (i.e., 30 mg, 3 times per week for up to 12 weeks; total dose >1,000 mg). Further, data from >10 years of post-marketing experience with Campath in >41,000 patients have also been analyzed (detailed in Appendix C, Section 10.3). These safety data allow for a more comprehensive understanding of the risks associated with use of alemtuzumab.

The sponsor performed an integrated analysis of safety including data from 6 analysis pools from MS clinical experience evaluating both 3-years of active-controlled data versus Rebif and through complete follow-up in all MS patients exposed to all doses of alemtuzumab. This pooled analysis of treatment emergent adverse events (AEs) from the Phase 2 and Phase 3 clinical studies indicated that:

- The overall incidence of AEs and SAEs were similar between treatment groups. The incidence of SAEs was 19.3% in the alemtuzumab 12 mg/day group and 19.4% in patients treated with Rebif.
- Fewer patients in the alemtuzumab 12 mg/day group (2.4%) than the Rebif group (7.9%) discontinued study treatment. Similarly, fewer patients in the alemtuzumab 12 mg/day group (0.3%) than in the Rebif group (4.2%) permanently discontinued study participation due to an AE.
- Infusion associated reactions (IARs), defined as any event occurring within 24 hours of an alemtuzumab infusion, and were frequent. The most frequent IARs (>10%) included headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills and flushing. Most IARs

were mild to moderate in severity and their incidence diminished over time (with subsequent infusions). Serious IARs were infrequent (2.8%) and very few led to treatment discontinuation (0.8%).

- Infections were frequent in both treatment groups. A total of 71.8% of patients treated with 12 mg/day alemtuzumab in all active-controlled studies experienced at least 1 infection compared with 54.2% of Rebif treated patients.
    - Frequent infections (>10%) in alemtuzumab-treated patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, and sinusitis. Most infections were mild to moderate in severity and responded to standard treatments. Serious infections were reported for 2.9% of alemtuzumab-treated patients versus 1.2% of Rebif treated patients. The most common serious infections on alemtuzumab (0.4%) were appendicitis, gastroenteritis, and pneumonia. There were no serious opportunistic infections.
    - There was no cumulative increase in the risk of infection with continued dosing or follow-up.
    - Herpes viral infections were more common in alemtuzumab treated patients than in Rebif treated patients (15.7% vs. 3.0%, respectively) driven by mucocutaneous herpes simplex and localized herpes zoster re-activation. The incidence of herpes simplex infections was reduced through the implementation of prophylaxis with acyclovir during the period of alemtuzumab infusion and continuing for 1 month thereafter.

Early experience with alemtuzumab suggested a potential risk for the development of antibody-mediated autoimmune AEs, as evidenced by the occurrence of ITP in the Phase 2 program, which prompted the implementation of risk minimization measures such as frequent lab monitoring and patient/physician education relative to symptom awareness in the clinical program. Periodic blood and urine tests were specifically performed to detect thyroid disorders, ITP and glomerular nephropathies of possible autoimmune etiology. A detailed review of the safety database (combining both the 12 mg and 24 mg/day dose groups over all available follow-up) was performed to comprehensively characterize the risk for autoimmune AEs. This review identified the following risks:

- Thyroid disorders: thyroid-related AEs were more common in the alemtuzumab 12 mg/day group (18.3%) compared to Rebif (5.4%). Most events were mild to moderate

in severity with similar incidences of hypo- and hyperthyroid AEs. The incidence of thyroid adverse events peaked during the third year of observations and decreased thereafter occurring in approximately 29% of alemtuzumab treated patients across 12 mg and 24 mg/day dose groups through all available follow-up.

- ITP: A total of 21 alemtuzumab-treated patients with medically confirmed ITP (Rodegheiro, 2009, *Blood*) were identified. Onset ranged from 1 to 28 months following last dose of alemtuzumab. With the exception of the index fatal case, which occurred prior to the implementation of specific risk minimization measures, all cases were detected through the monthly monitoring program, either by platelet counts or the early recognition of signs and symptoms allowing early treatment with most patients achieving a complete response from ITP within 3 months of diagnosis.

- Nephropathies: over all available follow up, 4 events of glomerulonephritis were identified in 4 patients in the 12 mg/day alemtuzumab dose group. These events occurred within 39 months following the last administration of alemtuzumab. The 4 cases of glomerulonephritis were reported as: glomerulonephritis membranous (2), anti-GBM glomerulonephritis (1) and Goodpasture's syndrome (1); all patients responded to medical treatment and none developed permanent kidney failure. All cases were detected through blood, urine and/or symptom monitoring implemented as part of risk minimization efforts.

The safety experience in the MS development program, in particular the intensive lab monitoring and symptom education efforts that led to the detection of all cases (following the index case of ITP) and allowed for prompt treatment, suggests these autoimmune disorders are readily identifiable through widely available lab tests, and are manageable when identified early. Specific safety measures used to identify, assess, and minimize the risks associated with alemtuzumab use, will be carried forward in the risk evaluation and mitigation strategy.

1.8 Summary of Risk Evaluation and Mitigation Strategy (REMS)

Genzyme has developed a comprehensive risk minimization program (detailed in Section 7) which includes a formal risk evaluation and mitigation strategy (REMS). Goals of the risk minimization program include:

- Education of patients and health care providers (via the REMS) about serious risks associated with the use of alemtuzumab (including symptom recognition)

- Mitigation of severity and sequelae of serious adverse events through early detection with periodic lab monitoring beginning prior to treatment initiation and continuing for 4 years after the last dose of alemtuzumab
- Continued surveillance for serious adverse events through a formal post-approval safety study

1.9 Conclusions

Alemtuzumab clinical trials in patients with RRMS demonstrated statistically significant and clinically meaningful reductions in the frequency of relapses, slowing of accumulation of disability, increased likelihood of a sustained reduction in disability, and benefit on diverse MRI endpoints; all are important measures of disease activity and indicators for future clinical outcomes. Alemtuzumab's treatment effects were demonstrated in randomized, rater-blinded, head-to-head studies over and above those of Rebif, an approved treatment for MS with demonstrated efficacy on the co-primary and imaging endpoints. Alemtuzumab increased the likelihood of improvement in disability (as measured by changes in EDSS and via SRD). Common AEs involved mild to moderate infusion reactions and infections which diminished over time and were generally managed through the use of prophylactic treatment and/or responded to conventional therapy. An important safety signal regarding the occurrence of autoimmune AEs was noted early in clinical development allowing Genzyme to pilot risk minimization measures including laboratory monitoring and patient and physician education. Such measures targeted thyroid disorders which occurred commonly but were largely non-serious events, and ITP and nephropathies which occurred much less frequently. These risks proved manageable when identified early via the monitoring program and were effectively treated.

In conclusion, the Phase 2 and 3 studies of alemtuzumab in MS clearly demonstrate a favorable benefit-risk profile in the populations studied. Alemtuzumab was shown to be highly efficacious both in patients who are naïve to treatment and in patients who had an inadequate response to prior therapies, a population for whom limited treatment options exist. Its brief dosing regimen of two annual treatment courses (12 mg/day for 5 days followed 12 months later by a further 3 days of treatment) may offer additional benefit through improved treatment compliance. With a unique mechanism of action and mode of administration, and a compelling efficacy profile established versus a high frequency, high dose interferon, alemtuzumab represents an important addition to the armamentarium of therapies at the disposal of neurologists treating patients with MS.

2. Background

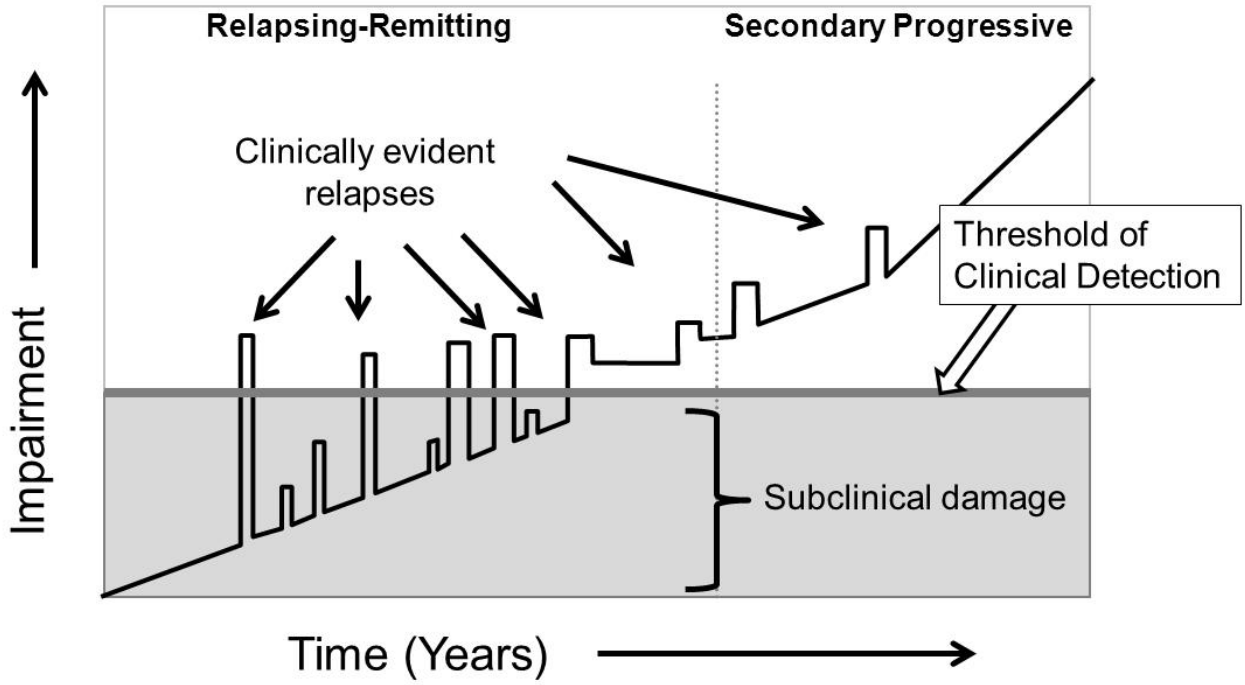
2.1 Multiple Sclerosis

MS is a chronic disorder of the CNS, involving brain, spinal cord and optic nerves. MS represents the leading cause of neurologic disability in young and middle-aged adults, affecting approximately 400,000 people in the United States (National Multiple Sclerosis Society, 2011). MS is more common among women than men and onset typically occurs between the ages of 20 and 50. The etiology of MS is unknown. Pathologically, MS is characterized by demyelinated plaques in the brain and spinal cord combined with inflammatory infiltrates consisting of lymphocytes (T cells and B cells) and activated macrophages/microglia; axonal loss and gliosis with astrocyte proliferation and glial fiber production are also noted (Lassmann, 1998, *Mult Scler*). This process, called demyelination, interrupts neuronal signalling and leads to the common symptoms of MS. There are some natural reparative processes, including remyelination, but they typically do not fully restore neuronal structure or function, and cannot compensate effectively if the demyelinated axon has been irreparably damaged.

Up to 80% of all MS patients present with RRMS (Noseworthy, 2000, *N Engl J Med*). The clinical course of RRMS typically manifests as initial episodes of transient neurological compromise (synonymously called relapses, clinical exacerbations or attacks) with variable recovery (remissions), eventually leading to cumulative deficits that may increase acutely with each new relapse episode. Common relapse symptoms include paresis (weakness) and incoordination, and impairments in gait, sensation (including vision), and bladder and bowel control.

Research has shown that clinically evident relapses are just the "tip of the iceberg" in terms of MS-related injury to the CNS. Inflammation is present from the earliest stages of RRMS, and causes damage that goes unnoticed (i.e., subclinical disease activity) except when it exceeds the body's compensatory mechanisms (Figure 1). Lesions that are large enough can be detected in clinically stable patients as new T2-hyperintense or gadolinium-enhancing lesions on magnetic resonance imaging (MRI) (McFarland, 1992, *Ann Neurol*), but even normal-appearing white and grey matter are microscopically abnormal (Frischer, 2009, *Brain*). Like relapses, subclinical disease activity cause demyelination and transection of neuronal axons, and contribute to brain atrophy and eventual disability.

Figure 1: MS-related CNS Injury



Over time, approximately 70% of patients with RRMS develop SPMS, characterized by deterioration that steadily worsens with or without superimposed relapses and is resistant to current therapies, leading to permanent disability. It is generally agreed that SPMS is a consequence of inflammatory tissue destruction accumulating during RRMS. Therefore, early therapeutic intervention to effectively suppress CNS inflammation is an important objective in the treatment of relapsing forms of MS.

2.1.1 Current Therapy for Multiple Sclerosis

Early intervention with disease modifying therapy (DMT) has become the standard approach to the management of relapsing MS. Approved DMTs are briefly summarized in Appendix A, Section 10.1. All of the currently approved MS DMTs target the disease via immune-based mechanisms of action attempting to reduce lymphocyte-mediated inflammation in the CNS with the goal of reducing the occurrence of acute exacerbations (relapses) and subsequent axonal injury and progression of physical disability.

Success in achieving these aims varies among currently approved DMTs. Neurologists may differ in their impression of the relative efficacy of available products since most have been studied in clinical trials only against placebo rather than in head-to-head comparisons.

A few head-to-head studies have been conducted among the MS DMTs. Most notably, a randomized, open-label, rater-blinded Phase 3 clinical trial showed Rebif® (subcutaneous IFNB-1a) reduced relapses and MRI lesions better than Avonex® (intramuscular IFNB-1a) supporting FDA approval of Rebif in the US (Panitch, 2002, *Neurology;* Rebif US Prescribing Information). No approved DMT has been shown to be more effective than Rebif in a randomized head-to-head study.

Two drugs that were approved after Rebif are believed by many to be more effective than other DMTs: these are Gilenya® (fingolimod) and Tysabri® (natalizumab). Gilenya, approved in 2010, was shown to be more effective in reducing relapses than Avonex in a 1-year head-to-head clinical study (Cohen, 2010, *N Engl J Med*). Impressions of Tysabri's relative efficacy are largely based on clinical experience and on results of a single placebo-controlled monotherapy trial and a second trial where Tysabri and Avonex were combined. However, no randomized active-controlled trials were conducted using the approved monotherapy regimen and neither drug has been shown to be more effective than any other in slowing the accumulation of disability. Further, both drugs carry risk of potentially serious complications, including elevated cardiac risk and macular edema associated with use of Gilenya, and risk for progressive multifocal leukoencephalopathy (PML) associated with use of Tysabri.

There are two common approaches to the treatment of relapsing MS. One approach is to initiate treatment with a DMT having modest efficacy but also a comparatively low risk of serious complications. Most patients use either beta-interferon or glatiramer acetate, which are sometimes referred to as "platform therapy" for MS. Patients who have inadequate response to initial therapy may be switched to another therapy, often another platform therapy delaying treatments with higher efficacy but increased risk.

Shortcomings of this escalation approach are increasingly being recognized. Many patients experience ongoing (or "breakthrough") disease activity during treatment with typical first-line DMTs, and suffer clinical relapses and also worsening subclinical disease in the form of an increasing burden of MRI lesions and brain atrophy (reviewed by Rudick and Polman, 2009). The adverse long-term implications of such breakthrough disease activity are becoming increasingly clear. For example, having an average of 1 relapse or 1 new enhancing MRI lesion per year during a 2-year clinical trial of IFNB-1a is predictive of near-term and long-term increased risk of disability progression (Rudick, 2004, *Ann Neurol*; Bermel, 2013, *Ann Neurol*; Rudick and Polman, 2009, *Lancet Neurol*). These clinical findings are further supported by evidence showing a causal link between brain inflammation and irreversible neurodegenerative

changes in MS, such as axonal transection (Frischer, 2009, *Brain*; Dutta, 2011, *Prog Neurobiol*). Thus, for many patients, delaying introduction of more (potent) effective therapy (potent) incurs a cost in the form of potentially permanent MS-related deterioration.

A different approach to treatment, increasingly favored by many MS experts, is to initiate treatment with a more efficacious DMT in patients at heightened risk for MS-related disability, whether treatment-naïve or already using a DMT. While methods for identification of patients at heightened risk of relapse and MS-related disability progression are still evolving, adverse prognostic indicators include severity, frequency and incomplete recovery from relapses, as well as measures of subclinical disease activity including the number of new or enlarging lesions on MRI and brain atrophy. For patients already receiving treatment with a DMT, the occurrence of relapse or subclinical MS disease activity (i.e. breakthrough disease) during treatment are established indicators of increased risk. In this approach, an individualized assessment of MS severity is considered together with knowledge of the efficacy and safety profiles of available DMTs and with a patient's attitudes about risk tolerance, and a treatment recommendation is thus tailored for each patient.

Given the need to individualize treatment recommendations, neurologists and patients are eager for additional RRMS treatment options. Further, given the high likelihood of breakthrough disease during treatment with current DMTs, there is a particular need for new, highly effective DMTs.

2.1.2 Unmet Medical Needs in the Management of Multiple Sclerosis

As noted above, many patients continue to experience disease activity despite treatment. Even a single MS relapse has the potential to result in irreversible injury and disability (Lublin, 2003, *Neurology*). Improved relapse prevention can, therefore, significantly improve patient outcomes and delay the accrual of permanent disability. The common occurrence of 'breakthrough' disease activity during DMT use highlights two important unmet needs in the treatment of patients with relapsing forms of MS that are potentially addressed by the development program for alemtuzumab:

- The need of drug-naïve patients for a treatment that will more effectively reduce the likelihood of relapse and the risk of disability, thus preventing breakthrough disease activity
- The need of patients using DMT but having breakthrough disease activity for a treatment that will more effectively reduce the likelihood of relapse and the risk of disability

Since no approved DMT regimen has been shown to reduce relapses or to slow disability progression more effectively than any other, a treatment proven to be more effective would represent an advance with potential to meet these needs, and an important addition to the existing range of treatment options for patients with RRMS.

2.2 Alemtuzumab Overview

Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen which is present at high levels on the surface of T and B lymphocytes and at lower levels on natural killer (NK) cells, monocytes, and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. The proposed mechanism of lymphocyte depletion is antibody dependent cell-mediated cytolysis and complement-mediated lysis following cell surface binding of alemtuzumab to lymphocytes (Bindon, 1988, *Eur J Immunol*; Hale, 1996, *Immunology*).

Research suggests that alemtuzumab alters the number, proportions, and properties of some lymphocyte subsets on repopulation (Cox, 2005, *Eur J Immunol*; Jones, 2009, *J Clin Invest*; Jones, 2010, *Brain*; Thompson, 2010, *J Clin Immunol*). The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not clearly defined, but may involve immunomodulation through the depletion and repopulation of lymphocytes.

Alemtuzumab was originally developed at University of Cambridge in the United Kingdom (Reichmann, 1988, *Nature*). As an agent that depletes lymphocytes, alemtuzumab was investigated early on for a variety of diseases including non-Hodgkin's lymphoma (Hale, 1988, *Lancet*), refractory vasculitic syndrome (Matheison, 1990, *N. Engl. J. Med*), rheumatoid arthritis (Weinblatt, 1995, *Arthritis Rheum*), graft versus host disease and prevention of bone marrow rejection (Hale, 2001, *Cytotherapy*; Kottaridis, 2001, *Cytotherapy*). Alemtuzumab was first approved by the FDA under BLA 103948 in 2001 for the treatment of fludarabine-resistant B-cell chronic lymphocytic leukemia (B-CLL) (Keating, 2002, *Blood*) and is known by the proprietary name Campath® for this indication. Campath was approved for first-line use in B-CLL in 2007 as part of an efficacy supplement filed to expand the indication. With its availability since 2001, Campath has been used in the course of medical practice in the treatment of other hematological malignancies, transplant rejection and demyelinating disorders, as well as for transplant conditioning.

Alemtuzumab development for MS began with open-label investigator-sponsored studies. A pilot study conducted in patients with secondary progressive MS (SPMS) found that

alemtuzumab caused significantly decreased annual relapse rates and the formation of lesions in the CNS (Moreau, 1996, *Mult Scler*). In a subsequent study in patients with RRMS, alemtuzumab produced sustained reductions in disability scores as well as sustained reductions in relapse rates and lesion formation (Coles, 2006, *J Neurol*), an effect not observed in patients with SPMS. The results of these studies suggested that alemtuzumab might be highly effective in patients with RRMS, prior to the occurrence of fixed deficits and progressive MS, which are believed to reflect axonal loss conditioned by prior inflammation (Trapp, 1998, *N Engl J Med*; Coles, 1999, *Ann Neurol*; Martinelli-Boneschi, 2004, *Mult Scler*). Observed side effects of alemtuzumab included frequent infusion-associated reactions (IARs) and infections (Moreau, 1996, *Mult Scler*; Coles, 1999, *Ann Neurol*), both consistent with the mechanism of action of alemtuzumab, as well as thyroid abnormalities (Coles, 2006, *J Neurol*). Thyroid disorders had not been commonly observed in clinical experience in patients with B-CLL.

2.2.1 Dose rationale

The proposed clinical dose of alemtuzumab is 12 mg/day IV for 5 consecutive days, followed 12 months later by 12 mg/day IV for 3 consecutive days.

The dosing in the pilot investigator-sponsored MS studies was guided by historical data from the use of Campath in oncology and by pilot studies in patients with rheumatologic disorders (Isaacs, 1992, *Lancet*; Weinblatt, 1995, *Arthritis Rheum*; Isaacs, 1996, *Br J Rheumatol*). The MS pilot studies were performed with 1 or 2 pulsed cycles of 20 mg alemtuzumab given over 3 or 5 days (total dose of 100 mg in cycle 1 and 60 mg in cycle 2). Each annual treatment cycle with alemtuzumab was administered in divided (daily) doses to improve tolerability, especially with regard to IARs (Moreau, 1996, *Brain*). The annual dosing interval was initiated given the observation that disease activity returned in some patients approximately 1 year after the previous treatment cycle. The retreatment dose (Cycle 2) was calculated as 60% of the initial dose, i.e., a 3-day cycle instead of a 5-day cycle (Cycle 1), to account for the reduced lymphocyte levels at Month 12 compared with baseline. It was noted that this treatment regimen significantly suppressed relapses and cerebral inflammation (measured by MRI) for at least 6 years (Coles, 2004, *Clin Neurol Neurosurg*). The subsequent selection of the dose and dosing regimen used in the Genzyme clinical program for patients with MS was based on these observations. Doses of 12 mg and 24 mg administered in 2 brief cycles approximately 12 months apart were selected for the Genzyme-sponsored Phase 2 study CAMMS223, which bracketed the 20-mg pilot study daily dose in MS patients.

Dose selection for the Phase 3 studies was based on the clinical data from CAMMS223. In Study CAMMS223, 2 annual cycles of both alemtuzumab 12 mg and 24 mg were significantly more effective than Rebif; additionally, the 12 mg and 24 mg doses had similar overall safety profiles. Because the patient populations in studies CAMMS223 and CAMMS323 were similar (i.e. treatment-naïve patients), the lower dose regimen shown to be effective in CAMMS223 (e.g. 12 mg) was carried forward in the confirmatory Phase 3 study CAMMS323.

The same dose regimen (12 mg) was also studied in CAMMS324; however, because the patient population in this study had a suboptimal response to prior MS therapy, the higher dose of 24 mg was also studied. However, randomization to the 24 mg arm was discontinued early in the study to reduce the duration of the enrollment period, which also reduced sample size and the overall duration of the study. The decision to close the alemtuzumab 24 mg/day arm to enrolment and did not involve review of Phase 3 efficacy or safety data

2.3 Regulatory History in MS

2.3.1 Phase 2 Study in MS

Work conducted at the University of Cambridge, UK (see Section 2.2), and other investigator-sponsored studies in MS, provided important evidence to allow further clinical investigation of alemtuzumab in MS and led to the design of a Phase 2 trial (CAMMS223) which Genzyme sponsored under an IND for MS submitted in October 2002.

During the Phase 2 study, 3 cases of ITP, including a fatal index case, were identified in 2005. Upon review of these events, the Data Safety Monitoring Board recommended that alemtuzumab dosing be suspended and Genzyme voluntarily adopted this recommendation. The Food & Drug Administration (FDA) was immediately notified relative to the proposed dosing suspension and a clinical hold for the IND was issued. The Agency requested modification to the protocol, Investigator Brochure, and Informed Consent Form to advise of the risk of ITP and to implement monitoring measures to decrease the risk to patients treated with alemtuzumab. Accordingly, Genzyme modified study documents as advised and developed a risk minimization plan for ITP to prevent morbidity and mortality potentially associated with this identified risk. A panel of hematologists was convened to assist in this effort. Patients remained on study and both investigators and patients were educated about ITP signs and symptoms, monthly monitoring for platelets by complete blood count testing was performed, and monthly patient surveys to detect early signs and symptoms of ITP were undertaken.

Communication with FDA regarding continued development of alemtuzumab eventually led to a Type B meeting in 2006 to outline measures necessary to resolve the clinical hold. In particular, FDA wanted to ensure that any further dosing occurred within the context of a study intended to provide evidence to definitively establish the safety and efficacy of alemtuzumab. They indicated that the hold could be lifted upon submission of a well-designed, well-controlled randomized study protocol. In contemplating the Phase 3 design, FDA suggested that, in consideration of the early safety profile of alemtuzumab, studies should be conducted in patients with an inadequate response to standard approved therapies for MS (i.e., beta interferon or glatiramer acetate).

With the submission of two Phase 3 study protocols in 2007, the clinical hold was lifted.

2.3.2 Phase 3 Clinical Program

The Sponsor submitted 2 Phase 3 protocols for FDA review under a request for Special Protocol Assessment (SPA). Phase 3 protocols (CAMMS323 and CAMMS324) proposed parallel multi-center, randomized, rater-blinded, active-controlled studies of alemtuzumab, as compared to Rebif, in patients with RRMS. The CAMMS323 study mirrored the design of the successful Phase 2 study CAMMS223 and included early, active patients who were naïve to prior disease modifying therapy in MS.

The CAMMS324 population was chosen in consideration of FDA's advice that alemtuzumab be evaluated in patients with an inadequate response to standard approved therapies for MS. Genzyme consulted a panel of neurologists with expertise in the treatment of MS in order to develop clinical eligibility criteria for CAMMS324 intended to select patients who had an adequate trial of a standard of care therapy but who continued to experience ongoing disease activity such that a change in their medical management may be appropriate (i.e., switching to another therapy seeking to reduce breakthrough activity). Based on this feedback, the CAMMS324 study was designed to evaluate alemtuzumab treatment in patients who experienced at least 1 relapse while previously treated with an MS disease modifying therapy for ≥ 6 months.

FDA agreed with the choice of Rebif as the active comparator, but strongly recommended a double-dummy, placebo-controlled design for the pivotal trials. At the time the Phase 3 trials were designed, high dose Rebif was a widely used standard of care for RRMS patients with active disease, or when switching from other platform therapies, given the effects superior to Avonex based on a head-to-head rater-blinded registrational study (Panitch, 2002, *Neurology*). In addition to superiority over Avonex, Rebif was also shown to delay the progression of MS

related disability versus placebo. Other available agents included Betaseron® (interferon beta-1b) and Copaxone® (glatiramer acetate), but neither had an established effect on disability progression (Betaseron US Prescribing Information; Copaxone US Prescribing Information). Finally, Rebif was shown to have beneficial effects on MRI outcomes in numerous clinical trials (PRISMS Study Group, 1998, *Lancet*; Li, 1999, *Ann Neurol*; Panitch, 2005, *J Neurol Sci*). Taken together, these efficacy data from clinical studies of Rebif set a high hurdle for a comparative treatment effect.

After thoroughly investigating options for a true double-dummy design using both placebo infusions and injections, it was determined that the only way to perform active-controlled study of alemtuzumab versus Rebif was through conduct of an open-label, rater-blinded study given the inability to manufacture a true matching placebo in the style of the proprietary Rebif syringe and given the well-known side effect profiles of both drugs (see further detail in Section 3.3). Further, there was precedent for use of rater-blinding in MS studies given the characteristic side effect profiles of each of the available MS products. With the decision to pursue a rater-blinded trial with Rebif as an active comparator, the SPA was not finalized.

Beginning with the initiation of discussions on the Phase 3 design and continuing throughout the clinical development phase, FDA expressed concern regarding the potential for introduction of bias given the open-label, rater-blinded design. Genzyme was advised to carefully assess the effectiveness of blinding (with particular reference to EDSS assessments performed to assess the primary disability endpoint) throughout the study to assure blinding was maintained and whether any unblinding events had influenced study results. FDA noted their support for the use of an independent relapse adjudication panel for both primary and sensitivity analyses of relapse. It was suggested that this approach could help ensure the quality of the relapse data and minimize the risk of bias. Following FDA's advice, care was taken to establish procedures to maintain blinding in the study documents (protocol, study operations manual, monitoring manual, informed consent form, etc.), to train site staff in order to ensure awareness of blinding requirements, to document blinding throughout the study and to assess events of unblinding and their potential impact on results through prespecified statistical analysis. A complete review of study procedures, training requirements, documentation methods and sensitivity analyses relative to the rater blind used in the Phase 3 program is provided Section 3.3.

The Statistical Analysis Plans (SAPs) for CAMMS323 and CAMMS324 were reviewed by the FDA. FDA provided feedback that was incorporated into revisions to the SAPs which were then

finalized and submitted to the IND prior to performing any statistical analysis of study data. FDA agreed to the analysis as presented in the final statistical analysis plans.

2.3.3 Supplemental Biologics License Application

A pre-sBLA meeting was held in January 2012 in order to discuss the content for the planned supplement in support of licensure of alemtuzumab in the treatment of MS. During this discussion, and in 2 subsequent letters to the Sponsor, FDA provided a detailed list of specific safety tabulations and reviewer aids (e.g., individual patient files and case narratives) to be performed for submission in order to augment those analyses outlined by the sponsor in the statistical analysis plans for each study. The Sponsor included this content in the supplement for alemtuzumab.

The supplement was originally submitted to the existing BLA for alemtuzumab in June 2012. FDA refused to file the supplement based on concerns that primarily related to the format of electronic datasets containing safety and efficacy data from the clinical development program. The Sponsor reformatted the electronic datasets for each clinical study included in the application and enhanced the detail provided in the documentation that accompanied these datasets in order to facilitate FDA review.

The supplement was resubmitted by the Sponsor in November 2012 and filed by FDA in January 2013. A standard review designation was assigned.

3. Phase 2 and Phase 3 Study Design

The Phase 2 and 3 studies were global, active-controlled, randomized, rater-blinded studies comparing the safety and efficacy of alemtuzumab to high-dose Rebif in patients with RRMS. All patients had active MS while studies CAMMS223 and CAMMS323 enrolled treatment-naïve patients and study CAMMS324 enrolled patients who had at least 1 relapse during prior treatment (for ≥ 6 months) with IFNB-1a or glatiramer acetate (Table 1).

Table 1: Alemtuzumab Clinical Development Program in MS

	Phase 2	Phase 3		Extension Study
	Study CAMMS223	Study CAMMS323	Study CAMMS324	Study CAMMS03409
Patients	334	581	840	1322
RRMS Population	Treatment naïve	Treatment naïve	Relapsed on prior treatment	CAMMS223 CAMMS323 CAMMS324
Study Duration	3 years (+ follow up)	2 years	2 years	up to 5 years
Treatment Arms	Alemtuzumab 12 or 24 mg Rebif 44 mcg	Alemtuzumab 12 or 24 mg Rebif 44 mcg	Alemtuzumab 12 or 24 mg Rebif 44 mcg	Alemtuzumab 12 mg (as needed after 2 fixed cycles)
Primary Endpoints	Relapse Rate & Sustained Accumulation of Disability			Long-term safety & efficacy

3.1 Study Design: Phase 2 Study CAMMS223

Study CAMMS223 was a Phase 2, active-controlled, randomized, rater-blinded, 3-arm study comparing alemtuzumab 12 mg/day or alemtuzumab 24 mg/day and Rebif in treatment-naïve patients with RRMS. The treatment-naïve patients in CAMMS223 were required to have early, active RRMS upon study entry (eligibility criteria are shown in Table 2).

Eligible patients were randomized in a 1:1:1 ratio to receive annual cycles of alemtuzumab 12 mg/day or 24 mg/day or Rebif 3 times weekly. Patients assigned to alemtuzumab received 5 daily IV infusions during Cycle 1 at Month 0, and 3 daily IV infusions during Cycle 2 at Month 12. Treatment with a third cycle (Cycle 3) of alemtuzumab administered at Month 24 was optional, at the discretion of the treating physician. Patients assigned to Rebif were to receive injections of 44 µg, 3 times a week from Month 0 through Month 24, after initial dose titration. The original study plan called for a 3-year treatment period, which was later extended by a follow-up period (making the total study period 5 or more years from entry) to support long-term monitoring.

3.2 Study Design: Phase 3 Program

CAMMS323 was designed as a 2 year, active-controlled, randomized, rater-blinded study to evaluate efficacy and safety of alemtuzumab versus Rebif. Similar to the Phase 2 study, treatment-naïve patients with early, active RRMS were enrolled, although unlike CAMMS223, patients in the Phase 3 study were not required to have ≥ 1 Gd-enhancing lesion on cerebral MRI at entry (Table 2). Patients were randomized in a 2:1 ratio to 2 annual cycles of 12 mg alemtuzumab or Rebif 3 times weekly.

CAMMS324 was a 2 year, active-controlled, randomized, rater blinded, dose blinded study comparing alemtuzumab 12 mg or alemtuzumab 24 mg with Rebif in patients with RRMS who had experienced at least 1 relapse during prior treatment with interferon beta or glatiramer acetate after having received that therapy for at least 6 months. Patients in CAMMS324 had MS symptoms for up to 10 years, an EDSS score of ≤ 5 and an MRI scan with abnormalities exceeding threshold criteria.

In an early amendment to the study, the alemtuzumab 24 mg/day arm was closed to enrolment in order to reduce the duration of the enrolment period, which also reduced sample size and the overall duration of the study. The decision to close the alemtuzumab 24 mg/day arm to enrollment was based on the observed patient recruitment rates and did not involve review of statistical analyses of Phase 3 efficacy or safety data.

3.2.1 Study Design: Extension Study CAMMS03409

Study CAMMS03409 is an ongoing, extension Study for eligible patients who participated in the Phase 2 and Phase 3 studies. Patients previously treated with alemtuzumab are subject to safety monitoring and may receive additional alemtuzumab (12 mg/day for 3 days) as needed upon documentation of resumed disease activity, defined as at least 1 protocol-defined relapse or at least 2 new or enlarging brain or spinal lesions on MRI. Alemtuzumab will not be administered within 48 weeks of previous alemtuzumab treatment. Patients previously treated with Rebif receive 2 annual cycles of alemtuzumab and may receive a third cycle as needed for resumed disease activity.

3.2.2 Inclusion/Exclusion Criteria

An overview of patient eligibility criteria for alemtuzumab clinical studies is provided in Table 2. Complete eligibility criteria are listed in Appendix B (Section 10.2).

Table 2: Overview of Patient Eligibility Criteria

Inclusion Criteria	CAMMS223	CAMMS323	CAMMS324
Patient Age (years)	18–50	18–50	18–55
Criteria for MS Disease Diagnosis	McDonald's update of the Poser criteria	McDonald's criteria	McDonald's criteria
Onset of MS Symptoms Prior to Study	Within past 3 years	Within past 5 years	Within past 10 years
Screening EDSS Score	0.0 to 3.0	0.0 to 3.0	0.0 to 5.0
MS Episode History	≥2 clinical episodes in prior 2 years	≥ 2 clinical episodes in prior 2 years with ≥1 episode in prior year	≥ 2 clinical episodes in prior 2 years with ≥1 episode in prior year
MS Treatment History	Treatment naïve	Treatment naïve	≥ 1 MS relapse during treatment with a beta interferon or glatiramer acetate after having been on that therapy for ≥ 6 months
MRI Findings	At least 1 Gd-enhancing lesion during any of up to 4 monthly screening MRIs	Cranial MRI scan demonstrating white matter lesions attributable to MS	Cranial MRI scan with white matter lesions attributable to MS plus at least 1 of the following 1) ≥ 9 T2 lesions ≥ 3 mm in any axis, 2) a Gd-enhancing lesion ≥ 3 mm in any axis plus ≥ 1 brain T2 lesions, 3) a spinal cord lesion consistent with MS plus ≥ 1 brain T2 lesions

3.2.3 Endpoints

A tabular listing of all primary and secondary endpoints used in the Phase 2 and Phase 3 studies is provided in Table 3.

Table 3: Efficacy Endpoints in CAMMS223, CAMMS323, and CAMMS324

Analysis Endpoints	CAMMS223 (Phase 2)	CAMMS323, CAMMS324 (Phase 3)
Primary Endpoint(s)		
Relapse Rate	X	X
Time to SAD (6-month criterion)	X	X
Secondary Endpoints		

Table 3: Efficacy Endpoints in CAMMS223, CAMMS323, and CAMMS324

Analysis Endpoints	CAMMS223 (Phase 2)	CAMMS323, CAMMS324 (Phase 3)
Proportion of patients relapse free	X	X
Change from baseline in EDSS (tertiary in CAMMS223)	X	X
Change from baseline in T2-hyperintense lesion volume	X	X
Change from baseline in MSFC (tertiary in CAMMS223)	X	X
Other Endpoints		
Time to first relapse	X	X
Relapse rate based on relapses treated with steroid therapy	--	X
Time to SAD (3-month criterion)	X	X
Worsened, stable or improved – EDSS	X	X
Time to SRD based on EDSS	--	X
Worsened, stable or improved – MSFC	X	X
Change from baseline in MSFC + Sloan	--	X
Worsened, stable or improved – MSFC + Sloan	--	X
New or enlarging T2-hyperintense lesions	--	X
New T1-hypointense lesions	--	X
Gd-enhancing lesions	--	X
Change from baseline in T1-hypointense lesion volume	--	X
Cerebral atrophy (secondary in CAMMS223)	X	X

All 3 active-controlled studies had the same 2 co-primary efficacy endpoints: relapse rate and time to 6-month sustained accumulation of disability (SAD [based on changes in EDSS]). These co-primary endpoints were supported by secondary and tertiary endpoints across the different domains.

3.2.3.1 Relapse

A relapse is an acute or subacute episode of new or worsening neurologic symptoms followed by a period of variable recovery and stability. The prevention of relapses is a fundamental goal of therapy for relapsing forms of MS. Severe relapses are typically treated with a 3-day course of glucocorticoid, usually 1,000 mg IV methylprednisolone for 3 or 5 days.

The annualized relapse rate (i.e., number of relapses per patient-year) was a co-primary endpoint in all clinical studies of alemtuzumab in MS and has been commonly accepted as a reliable measure of therapeutic effect in MS clinical trials (Steinvorth, 2013, *Mult Scler*). In fact, all previous Phase 3 studies of disease modifying therapies (DMTs) in MS have included the effect

on relapse rate as an efficacy endpoint, and for most DMTs the effect on relapse rate served as the primary efficacy endpoint for drug approval.

A secondary relapse endpoint was the percentage of patients with no relapses during the study (relapse-free). Additional relapse-related measures included relapse severity, hospitalization for relapse management, and relapses treated with steroids.

MS relapse in the alemtuzumab program was defined in the study protocols as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must be attributable to MS, last at least 48 hours, be present at normal body temperature, and be preceded by at least 1 month (30 days) of clinical stability.

Per McDonald diagnostic criteria for MS (McDonald, 2001, *Ann Neurol*; Polman, 2005, *Ann Neurol*), the neurological disturbance of a relapse should last for at least 24 hours. The more stringent 48-hour criterion used by Genzyme has also been used in randomized, controlled studies with some other DMTs (Johnson, 1995, *Neurology*; Jacobs, 1996, *Ann Neurol*; Miller, 2003, *N Engl J Med*; Comi, 2012, *N Engl J Med*) and was selected to reduce the chance that minor or transient symptoms would be mistaken for a relapse.

Care was taken in Genzyme's studies to ensure that all potential relapses were similarly evaluated. The protocol required that new or worsening neurological symptoms were reported to the treating neurologist or nurse within 48 hours of onset and a comprehensive relapse assessment was to occur within 7 days of onset unless it was very clear that symptoms were not MS related. Relapse evaluation included an EDSS exam performed by the blinded rater and a subsequent physical exam performed by the treating neurologist. The treating neurologist also arranged for supportive laboratory testing if indicated, and could initiate standardized treatment with corticosteroids per protocol.

In both Phase 3 studies, all potential relapses were evaluated by a blinded RAP and only relapses confirmed by the RAP were considered in the calculation of relapse endpoints (see Section 3.3.5 for further detail on the RAP).

3.2.3.2 Disability

Severe disability arising from neurological impairments is the feared end-stage of MS. Disability early in the course of disease is generally the result of incomplete recovery from clinical attacks, even from a first attack. The level of impairment visible from an attack may

appear mild or moderate in degree even though the disease itself continues to progress subclinically.

Expanded Disability Status Scale **(EDSS)**. The EDSS (Kurtzke, 1983, *Neurology*) is an ordinal scale for the assessment of impairment and disability in MS and has served as the most widely used disability scale in clinical trials (Cohen, 2012, *Lancet Neurol*). EDSS is scored quantitatively based on objective findings from a standardized neurological examination. The scale begins at 0 (normal neurological exam) and ranges to a maximum of 10 (death from MS) through a series of steps, each explicitly defined by the degree of impairment on 7 neurologic functional systems and by ambulation. The 7 functional systems (FS) are: Visual, Brain Stem, Pyramidal, Cerebellum, Sensory, Bowel & Bladder, and Cerebral. In fully ambulatory patients, changes in pyramidal and cerebellar FS tend to be the greatest contributors to sustained EDSS progression, although all of the FS are important in understanding the overall impact of MS progression (Scott, 2011, *Neurol Res*). An increase in FS or EDSS score indicates a worsening of disability, whereas a reduction in score indicates an improvement.

In all Genzyme studies, certified trained raters who were blinded to treatment assignment documented the EDSS evaluations conducted at baseline and quarterly visits with no reference to previous scores. These quarterly assessments occurred according to the protocol-specified schedule, regardless of relapses, and formed the basis for analysis of the co-primary endpoint of 6-month SAD and all other EDSS-based endpoints.

Blinded raters in alemtuzumab studies received standardized training in properly scoring the FS and EDSS according to the Neurostatus system (neurostatus.net), which has been used in nearly all multi-centre MS studies in the last years. With careful assessment by trained examiners, the expected variability in clinically stable patients is very small. Moreover, in the early MS population, patients may recover from relapses so their post-relapse FS/EDSS scores may be identical to baseline.

Sustained accumulation of disability **(SAD)**. The standard for a demonstration of efficacy on MS-related disability has been a differential effect on SAD, in which a post-baseline $\geq$ 1 point increase in EDSS score is re-confirmed at a subsequent visit, generally after an interval of 3 or 6 months. (Other trials have used this same definition but called their endpoint "confirmed disability progression", "sustained disability progression", or synonymous terms.) A sustained 1 point change in EDSS is considered to represent a clinically significant deterioration or improvement in disability for an individual patient (Amato, 1988, *Arch Neurol*). Confirmation

of sustained disability change is important to ensure that an observed increase represents a persistent change in a patients' performance status, rather than a transient fluctuation in score due to patient fatigue or illness, or to variability in a rater's assignment of EDSS score.

Time to 6-month SAD was chosen as the primary disability endpoint in Genzyme studies. The 6-month criterion was selected over the 3-month definition because this longer requirement has greater predictive value for the development of irreversible disability (Liu, 2000, *J Neurol Neurosurg Psychiatry*).

***Sustained reduction in disability* (SRD)**. The SRD endpoint scores events in which there is a sustained improvement in pre-existing disability. SRD was defined as a ≥ 1 point decrease in EDSS score lasting ≥ 6 months, and was scored for patients with pre-existing disability at baseline defined as EDSS score ≥ 2.0 (Phillips, 2011, *MS Journal*).

***Multiple sclerosis functional composite* (MSFC)**. Disability was also assessed by blinded raters using the MSFC. The MSFC includes three objective subscales that evaluate ambulation, hand/eye coordination and dexterity, and cognition:

- 25-foot timed walking test: time (in seconds) that patients take to walk 25 feet as quickly as possible without running
- Nine hole peg test: mean time (in seconds) to insert and remove 9 pegs, with right and left arms scored separately
- Paced Auditory Serial Addition Test-3 second version (PASAT-3): number of correct answers by adding 60 serial single digit numbers, provided every 3 seconds.

The scores for these 3 components are combined to create an overall z-score.

Sloan Low-Contrast Visual Acuity. While the standard MSFC does not currently include a test of visual function, Sloan Low-Contrast Visual Acuity charts can be incorporated into the MSFC as a fourth subscale (Balcer, 2000, Mult Scler; Balcer, 2003, Neurology). This MSFC-4 yields a single composite disability score that is sensitive to visual dysfunction. The Sloan charts were not administered to patients at sites where the Cyrillic alphabet is the native standard since the charts use Latin alphabetic characters that may have been unfamiliar to individuals in these countries.

Imaging. MRI offers a highly sensitive, objective and quantitative measurement of brain and spinal cord structures and lesions that complement clinical assessments of MS. MRI findings

have served as supportive evidence of therapeutic effect in Phase 3 studies for all currently approved MS therapies.

In Genzyme studies, imaging endpoints included changes in T2 lesion volumes, measurements of lesion number and activity (for T2 hyperintense, Gd-enhancing, and T1 hypointense lesions), and measurement of brain atrophy.

T2-hyperintense lesion volume reflects the inflammatory demyelination and edema characteristics of active MS lesions, as well as the sclerotic gliosis of end-stage MS plaques. Gadolinium-enhancing lesions result from blood-brain barrier disruption secondary to acute inflammation and represent active inflammation at the time of the MRI scan. T1-hypointense lesions include foci where axonal density has been permanently reduced by MS-related tissue destruction.

Brain parenchymal fraction is the ratio of brain matter to total cerebral volume (Fisher, 2002, Neurol) and its serial measurement provides a sensitive indication of brain atrophy. Individuals with MS typically show a faster decline in whole brain volume over time compared to the general population due to disease-related destruction of neuronal and oligodendroglial tissue.

3.3 Blinding

The choice of Rebif as an active comparator provided a robust assessment of the benefit/risk profile of alemtuzumab versus an effective MS treatment, but precluded a double-dummy study design. Rebif 44 µg was commercially available only in proprietary prefilled syringes that prevented the ability to create a matching placebo. There are also substantial differences between alemtuzumab and Rebif in timing and mode of administration and side effect profiles. During the annual cycles of alemtuzumab IV infusions, nearly all patients experience infusion-associated reactions (Moreau, 1996, *Brain*), which often include headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, chills, flushing, fatigue, dyspnea, generalized rash, and dizziness. With a markedly different time and mode of administration (3-times weekly self- or other-administered by SC injection), Rebif also has a distinct safety profile, with many patients experiencing injection site reactions and flu-like symptoms (Rebif US Prescribing Information, 2011). These characteristic side effect profiles of both drugs, most notably the lymphopenia that results from the pharmacodynamic effect of alemtuzumab that would be evident upon routine lab testing, would likely subvert a double-blind study design.

Therefore, key efficacy assessments were performed by trained disability raters who were blinded to treatment assignments and had no access to patient study data (i.e., no data fields were reported to the blinded rater).

In the Phase 2 Study CAMMS223, disability endpoints based on the EDSS were determined by a blinded rater. The blinded rater documented an examination and an EDSS with no reference to previous records. The blinded rater also performed the EDSS for the purposes of potential relapse assessment. After completing the neurological assessment, the blinded rater could refer to records of previous neurological examinations to determine if a relapse had occurred. Study personnel were trained on the procedures to maintain blinding at study initiation and protocol defined procedures were reviewed at Investigator meetings.

In the Phase 3 studies, additional documentation and training on blinding procedures was implemented from the time of study initiation in order to enhance protocol defined procedures intended to maintain blinding. Through these efforts, the integrity of rater blinding was preserved by specific training on study roles and responsibilities, detailed documentation and protocol defined procedures regarding the blinding of efficacy assessments, ongoing monitoring of blind integrity throughout the study and limited access to study data on the part of Genzyme. No efficacy data sets or summaries with treatment group information were ever produced by the sponsor prior to database lock. In addition, Genzyme had written instructions for maintaining the integrity of the blinded clinical trial data across functional areas involved in study conduct and data analysis. Specific study blinding elements incorporated into the Phase 3 program are detailed in the sections that follow.

3.3.1 Blinded Assessment of Disability Endpoints

In the Phase 3 studies, each study site was required to have a primary blinded rater to perform all EDSS assessments from which the key disability endpoints were determined (i.e., SAD, SRD and change from Baseline in EDSS). EDSS assessments were performed at quarterly visits as part of the evaluation of disability endpoints. The blinded rater also performed EDSS evaluations on an unscheduled basis at the time of a suspected relapse. Each site was also required to identify a back-up blinded rater who was to replace or substitute for the primary blinded EDSS rater if he or she were to become unblinded or was unavailable to perform a blinded assessment. All EDSS raters were physicians with a minimum of 2 years of neurology training or experience, or other licensed health professionals (e.g. nurse practitioner, physician assistant or similar clinician) with at least 2 years prior experience performing similar exams. All EDSS raters were required to be certified on the conduct of the EDSS.

The blinded rater had no access to patient data and did not record data directly into the study case report form. Since the EDSS rater was to remain blinded throughout the course of the study, no data fields were accessible to the blinded EDSS rater and they performed each exam without reference to prior EDSS score.

Under the initial Phase 3 protocols, in exceptional circumstances where a blinded rater was not available and only in the case of a suspected relapse, unscheduled EDSS assessments could be performed by the unblinded treating neurologist. In February 2010, a letter was issued to all sites, which instructed that unscheduled EDSS assessments performed by unblinded personnel as part of a relapse evaluation were no longer permitted. The protocol was also amended to reflect this change in procedure.

3.3.2 Training Procedures

In the Phase 3 studies, all study staff, including blinded raters, were trained on requirements for maintaining the blind. The critical importance of all blinded raters remaining unaware of patients' treatment assignments for the duration of the study was emphasized. Sites were initially trained at study initiation visits and/or investigator meetings. At these meetings, detailed blinding instructions which included the precautions for all site personnel, blinded raters, and patients, as described in the protocol and study operations manual, were reviewed with site staff. Refresher training was mandated to ensure compliance and awareness because of the importance of maintaining rater blinding. This training was mandatory for all members of the site study team, both blinded and unblinded staff. Investigator meetings were conducted throughout the study period, both face to face and electronically (webinars throughout the study). Maintenance of the blind was always an important component of such meetings in order to provide continued guidance relative to compliance with study blinding procedures.

3.3.3 Documentation of Blinding Procedures and Instances of Unblinding

The specific procedural elements designed to ensure maintenance of the blind were documented in the individual study protocols and study operations manuals, and reiterated in training materials. These documents clearly noted that blinded raters were to perform a structured neurological exam with no reference to previous records. Blinded raters were also required to avoid contact with study patients except when performing the blinded EDSS assessment. Blinded raters were instructed to restrict questions and comments to those necessary for completing the EDSS. At the start of each blinded assessment, blinded raters were instructed to remind subjects not to reveal which treatment they were receiving or discuss their disease or any other medical history that might inadvertently reveal the patient's treatment assignment.

All study personnel were to be aware of the specific individuals serving as blinded raters and were instructed to avoid inappropriate conversation (e.g., regarding a patient's AEs) in their presence. Further, unblinded study site personnel were instructed not to leave patients' clinical information (e.g., laboratory results) in plain view. Site personnel were to provide the patient with adequate covering/clothing for the EDSS exam to mask marks on their body that could allow the identification of the study drug being received (e.g. an injection mark).

All patients were to be informed of which individuals at the study site were blinded raters and instructed to avoid inappropriate conversations in the blinded rater's presence (e.g., discussions of their symptoms or reactions which might indicate the treatment they were receiving). Patients were also instructed to respond only to questions from the blinded rater that were asked during the conduct of a blinded assessment. Documents and educational materials supplied to study patients, including the Informed Consent Form contained reminders about the importance of the blind.

In order to prospectively document any events of unblinding that should occur over the course of study, the Phase 3 program included documentation of the EDSS rater's blinding status at each patient's Month 12 and Month 24 (or early discontinuation) visit. During the course of the studies, a worksheet was added to allow the blinded rater to document their status at each visit where an EDSS was performed. Since the worksheet was instituted after study start, some of this information was collected retrospectively.

Per study protocol, blinded raters were instructed to immediately notify the Principal Investigator should they become unblinded at any point, and a trained, certified back-up rater was to perform all subsequent evaluations of the patient for whom the blind had been broken. Any issues noted upon Sponsor monitoring relative to maintenance of blinding procedures were to be reviewed with study staff, including the Principal Investigator, at the conclusion of each monitoring visit. These monitoring practices were designed to augment training and documentation efforts and to provide continuous instruction relative to the importance of blinding.

3.3.4 Analysis

In order to carefully assess the robustness of efficacy outcomes, the statistical analysis plan for the Phase 3 studies pre-specified several sensitivity analyses to evaluate the potential effect of any events of unblinding on the primary efficacy endpoints (Section 3.4).

3.3.5 Relapse Adjudication Panel (RAP)

The Phase 3 studies included an objective definition of relapse and a standardized procedure for assessment of all suspected relapses as described in Section 3.2.3.1. Neither the blinded rater nor the treating physician made a determination of whether a suspected event actually constituted a relapse. Instead, an independent, blinded RAP made all relapse determinations in the Phase 3 studies. The RAP reviewed all suspected on-study relapses (i.e., new or worsening neurological symptoms) and all potential events were sent to the RAP regardless of whether the treating investigator considered the patient's symptoms to be the result of a relapse.

The RAP was comprised of 6 independent neurologists with expertise in MS clinical research who were not investigators in any other Genzyme-sponsored studies with alemtuzumab. The RAP members were trained on study procedures by the Sponsor and an independent Contract Research Organization (CRO) who managed all RAP activities throughout the study. RAP members were required to review trial data and perform adjudications in accordance with the protocol- specified definition (see Section 3.2.3.1).

Genzyme transferred blinded data that were relevant to assessment of relapses to the CRO, who prepared blinded case dossiers to be reviewed by the RAP via a secure electronic portal. The dossiers included a standardized listing for each suspected relapse that specified onset date, type and severity of reported symptoms, whether the event had disqualifying characteristics (e.g., lasted <48 hours, or symptoms not MS-related), and whether event was treated with methylprednisolone. The dossiers also included vital signs, AEs related to the potential relapse, physical examinations, and EDSS scores with all supporting data from the standardized Neurostatus exam; values from baseline and the most recent prior quarterly assessment were provided as context for values from the relapse evaluation visit. Medical/surgical history and clinical episode history were also provided. In order to minimize the potential for inclusion of data which could potentially unblind an individual case under review (e.g. inclusion of adverse event with details that could suggest a treatment assignment), the CRO performed additional programmatic checks on text fields pertaining to Adverse Events and Physical Examination findings for data points that were part of the relapse case listing.

Each potential relapse was reviewed by 2 RAP members who worked and entered their evaluations independently, on cases randomly assigned to them by the CRO. The RAP adjudicated each case based on all available data provided for that case and members were not permitted to contact the site or the sponsor for additional information. If 2 RAP reviewers reached the same decision as to whether an episode constituted a relapse, the decision was

recorded by the CRO. If the 2 reviewers provided a conflicting assessment, a third RAP member reviewed the case so that a majority vote could be obtained. The majority vote of up to 3 RAP members served as the final determination as to whether an event met criteria for an on-study protocol defined relapse.

Relapse determinations by the RAP were not communicated to study sites, and the RAP had no involvement in patient management decisions. For each Phase 3 study, the results of RAP adjudications were transferred to the Sponsor only after the last patient completed the study. The Sponsor had no knowledge of RAP adjudications while the studies were ongoing.

3.3.6 MRI

All cranial MRIs were evaluated by neuroradiologists at an independent central facility with no access to patients' treatment assignment and the results of these evaluations were not provided to study sites.

3.4 Statistical Methods

3.4.1 Phase 3 Studies CAMMS323 and CAMMS324

The CAMMS323 and CAMMS324 statistical analysis plans were reviewed by the FDA and their content agreed upon prior to any analysis by the Sponsor.

The Full Analysis (FA) set, consisting of all treated patients, was the primary analysis population for efficacy in these studies.

3.4.1.1 Endpoints

Relapse rate

Treatment group comparisons for the relapse rate co-primary endpoint were performed using the Anderson-Gill model (an extension of the Cox proportional hazards model to the recurrent event setting) with treatment and geographic region as covariates and robust variance estimation. Patients who withdrew prior to treatment were not in the FA set or in the primary analysis. Treated patients who withdrew from the study were censored at the time of study discontinuation. Annualized relapse rates were estimated using a negative binomial model with treatment group and geographic region as covariates and log of follow-up as an offset. The onset date of relapse symptoms was used in the calculation of the relapse rate.

Sensitivity analyses (pre-specified and post-hoc) assessed the potential impact of the rater-blinded study design on the primary relapse analysis including analyses focusing on patient discontinuation and EDSS assessments performed by unblinded raters.

Time to 6-month SAD

Treatment group comparisons for the co-primary endpoint, time to 6-month SAD, were performed using the Cox proportional hazards model with treatment group and geographic region as covariates and robust variance estimation. Treated patients who withdrew from the study had their follow-up censored at the time of study discontinuation. The Kaplan-Meier method was used to estimate the percentage of patients experiencing SAD.

The relapse rate sensitivity analyses were also performed on the time to SAD endpoint. Additional sensitivity analyses included replacing the unblinded EDSS result with the most recent blinded EDSS plus some increment assuming unblinded rater bias and multiple imputation to account for patient dropout.

3.4.1.2 Other endpoints

The secondary efficacy endpoints were proportion of relapse-free patients, EDSS change from baseline, percent change in MRI T2-hyperintense lesion volume and MSFC change from baseline. Table 3 provides a complete list of endpoints for the Phase 3 studies.

Additional efficacy endpoints included time to 6-month sustained reduction in disability based on the EDSS and other MRI endpoints.

3.4.1.3 Multiple testing adjustments

The co-primary efficacy endpoint analysis was adjusted for multiple comparisons via the Hochberg method. Using this method, each study was to be considered to have met its primary efficacy objective if the p-values corresponding to the analysis of the primary endpoints satisfied at least 1 of the following conditions: the maximum of the 2 p-values is ≤ 0.05; the minimum of the 2 p-values is ≤ 0.025. Therefore, each study would be considered to have met its primary efficacy objective if a statistically significant difference between alemtuzumab and Rebif is observed in time to SAD and/or relapse rate.

Hypothesis testing for the secondary efficacy endpoints was performed using a closed testing procedure with the following rank order:

- Proportion of patients relapse-free at Year 2

- Change from baseline in EDSS
- Percent change from baseline in MRI-T2 hyperintense lesion volume at Year 2, and
- Acquisition of disability as measured by MSFC

3.4.1.4 Power and sample size

For study CAMMS323, approximately 525 patients were to be randomized in a 2:1 ratio to alemtuzumab 12 mg/day or Rebif which provided ≥ 95% power to detect the expected treatment effect in relapse rate and SAD. The assumptions for the time to SAD endpoint included: 20% of Rebif patients experience SAD by 2 years, 10% dropout and a 60% alemtuzumab treatment effect.

Under the original protocol for CAMMS324, the study was dose blinded for alemtuzumab and patients were randomized in a 2:2:1 ratio to receive alemtuzumab 12 mg or 24 mg or Rebif. A sample size of 1200 patients was planned in order to provide >80% power to detect a 45% treatment effect in time to SAD, assuming 20% of Rebif patients experience SAD by 2 years and 10% dropout.

The 20% 2-year SAD assumption for Rebif was based on the Phase 2 study (CAMMS223) and was consistent with other studies (Ebers, 1998, *Lancet*; Panitch, 2002, *Neurol*; Mikol, 2008, *Lancet Neurol*).

In an early amendment to the study (Amendment 2), the alemtuzumab 24 mg/day arm was closed to enrolment in order to reduce the duration of the enrolment period, which also reduced sample size and the overall duration of the study. Randomization continued at a 2:1 ratio to alemtuzumab 12 mg/day and Rebif until approximately 382 patients were assigned to alemtuzumab 12 mg/day and 191 were assigned to Rebif. This sample size provided >80% power to detect a 50% treatment effect in time to SAD given a 2-year SAD rate of 20% for the Rebif patients. The 50% treatment effect was used because in the CAMMS223 study alemtuzumab reduced the risk of SAD by 71% compared with Rebif. The decision to close the alemtuzumab 24 mg/day arm to enrollment was based on the observed patient recruitment rates and did not involve any statistical analysis of Phase 3 efficacy or safety data.

While relapse is a recurrent event, sample size estimation for the relapse rate co-primary efficacy endpoint was approximated using the time to first relapse endpoint. Assuming 68% of patients treated with Rebif relapse in 2 years, a hazard ratio of 0.60 comparing alemtuzumab with Rebif, a 2-sided significance level of 2.5% (second step of Hochberg procedure), and the other

assumptions made for the time to SAD endpoint, the power for detecting a treatment difference in the relapse rate endpoint is >95%.

4. Overview of Efficacy

This section describes the results of 3 randomized, active-comparator studies (Phase 2 Study CAMMS223 and Phase 3 studies CAMMS323 and CAMMS324) that have been completed as well as the ongoing Extension Study CAMMS03409.

4.1.1 Phase 2 Study CAMMS223

4.1.1.1 Patient Disposition

In Study CAMMS223, 334 patients were randomized. Approximately 85% of alemtuzumab-treated patients completed 3 years of follow-up compared to 61.7% of the Rebif-treated patients. This imbalance of completion was principally due to the protocol originally allowing study discontinuation when SAD was reached. The full analysis set consisted of all randomized patients who had a confirmed diagnosis of MS (111 in Rebif, 112 in alemtuzumab 12mg/day and 110 in alemtuzumab 24mg/day).

While the primary efficacy analysis was conducted at 3 years, the study was extended to allow for additional monitoring. Approximately half of the originally enrolled alemtuzumab-treated patients, 109 (51%) had >5 years of total follow-up. The overall person-years of follow-up were 376 for Rebif treated patients and 480 for alemtuzumab treated patients.

4.1.1.2 Baseline Demographic and MS Disease Characteristics

Demographic and MS disease characteristics were well balanced across treatment groups (Table 4). The disease-related baseline characteristics indicate that an early, active disease population was enrolled into the study.

Table 4: Baseline Demographic and MS Disease Characteristics, Study CAMMS223 Full Analysis Set

	IFNB-1a (N=111)	Alemtuzumab 12 mg/day (N=112)	Alemtuzumab 24 mg/day (N=110)
Age (years)			
Mean (SD)	32.8 (8.82)	31.9 (8.01)	32.2 (8.76)
Median	31.0	31.0	31.0
Min, Max	18.0, 60.0	18.0, 49.0	18.0, 54.0
Sex, n (%)			
Male	40 (36.0)	40 (35.7)	39 (35.5)
Female	71 (64.0)	72 (64.3)	71 (64.5)
Race, n (%)			
White	100 (90.1)	102 (91.1)	98 (89.1)
MS History (time since first episode, years)			
Mean (SD)	1.6 (1.01)	1.4 (0.84)	1.5 (0.84)
Median	1.4	1.3	1.2
No. of relapses in prior 2 years, n (%)			
0	0	2 (1.8)	1 (0.9)
1	8 (7.2)	5 (4.5)	13 (11.8)
2	73 (65.8)	58 (51.8)	56 (50.9)
≥ 3	30 (27.0)	47 (42.0)	40 (36.4)
Baseline EDSS			
Mean (SD)	1.9 (0.81)	2.0 (0.73)	2.0 (0.73)
Median	2.0	2.0	2.0
Min, Max	0.0, 3.5	0.0, 3.0	0.0, 3.5

4.1.1.3 Relapse

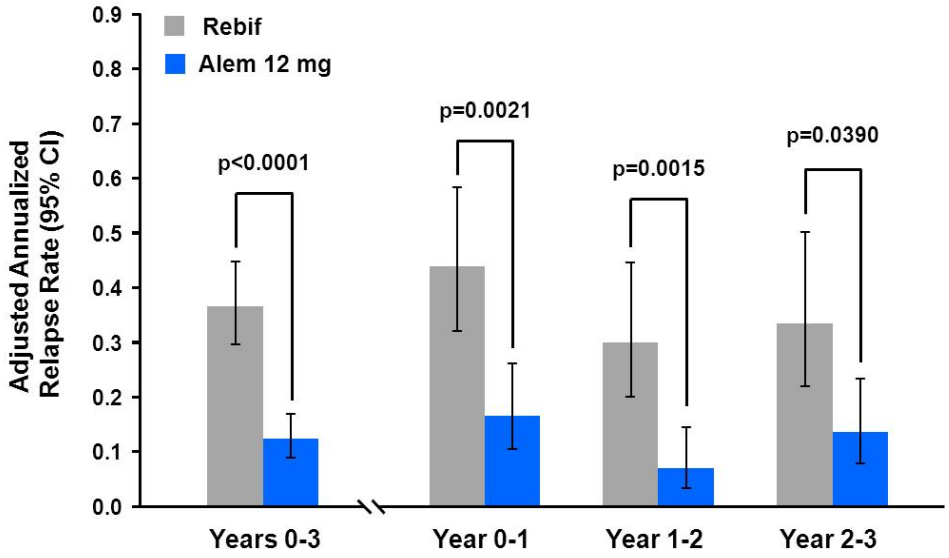
Alemtuzumab 12 mg/day reduced the relapse rate by 67% compared with Rebif over 3 years ($p < 0.0001$, Table 5 and Figure 2). The percentage of patients experiencing a relapse by Year 3 was 24% for alemtuzumab 12 mg/day and 50% for Rebif. The effect of alemtuzumab 24 mg/day on relapse was not substantially different than alemtuzumab 12 mg/day.

Table 5: Relapse Rate and Treatment Effect Summary (3 Year Follow-Up), Study CAMMS223 Full Analysis Set

Statistic	IFNB-1a (N=111)	Alemtuzumab 12 mg/day (N=112)	Alemtuzumab 24 mg/day (N=110)
Patients with events, n	47	25	18
Total number of events	91	38	29
ARR (95% CI)	0.37 (0.30, 0.45)	0.12 (0.09, 0.17)	0.09 (0.06, 0.13)
Rate ratio (95% CI)	--	0.33 (0.20, 0.55)	0.23 (0.13, 0.43)
Treatment effect	--	67%	77%
p-value	--	<0.0001	<0.0001

Rate ratio and p-value calculated using Anderson-Gill model with treatment group, baseline EDSS and country as covariates and empirical variance estimation. ARR estimated by Poisson regression with treatment group as a covariate and log of study follow-up time as an offset.

Figure 2: Annualized Relapse Rate, Study CAMMS223 Full Analysis Set



4.1.1.4 Disability

Time to 6-month SAD

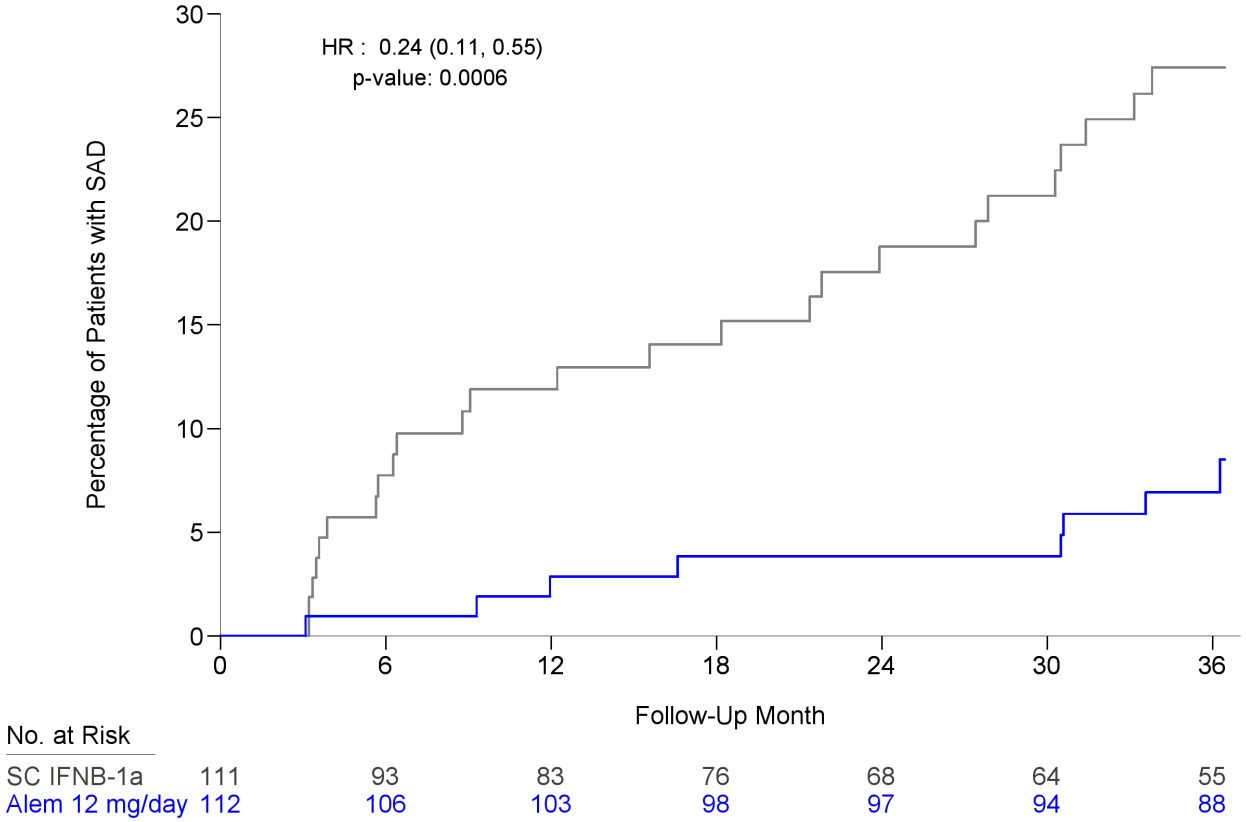
Alemtuzumab 12 mg/day reduced the risk of SAD by 76% as compared to Rebif (p=0.0006) over 3 years. Again, the effect of alemtuzumab 24 mg/day on SAD was not substantially different compared with 12 mg/day (see Table 6 and Figure 3).

Table 6: Time to 6-Month SAD and Treatment Effect (3 Year Follow-Up), Study CAMMS223 Full Analysis Set

Statistic	IFNB-1a (N=111)	Alemtuzumab 12 mg/day (N=112)	Alemtuzumab 24 mg/day (N=110)
Proportion of patients	0.27 (0.19, 0.38)	0.08 (0.04, 0.17)	0.09 (0.05, 0.17)
Hazard ratio (95% CI)	--	0.24 (0.11, 0.55)	0.31 (0.15, 0.66)
Treatment effect	--	76%	69%
p-value	--	0.0006	0.0021

Hazard ratio and p-value calculated from proportional hazards model with treatment group, baseline EDSS and country as covariates.
Proportion of patients experiencing SAD estimated via Kaplan-Meier method.

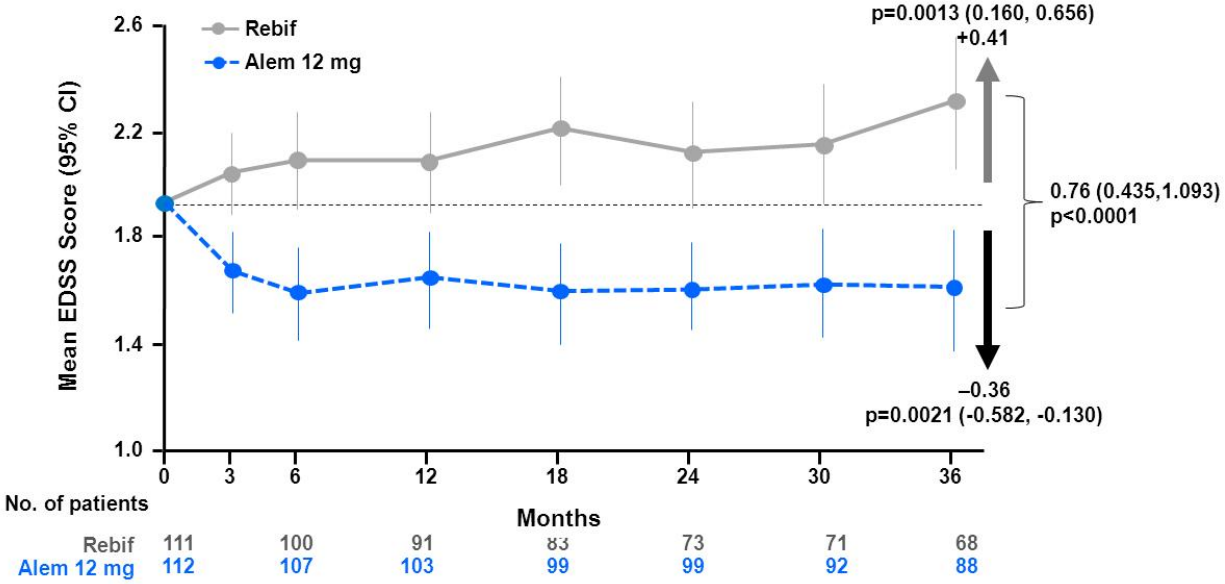
Figure 3: Kaplan Meier Estimate of Time to 6-Month SAD, Study CAMMS223 Full Analysis Set



EDSS change from baseline

Alemtuzumab treatment also resulted in an improvement from baseline in the mean EDSS score (Figure 4). These changes from baseline (improvement for the alemtuzumab 12 mg/day group and worsening for the Rebif group) and the between group differences were significant ($p<0.0001$). These data suggest that, alemtuzumab treatment may improve neurological symptoms representative of disability in MS patients.

Figure 4: EDSS Change from Baseline, Study CAMMS223 Full Analysis Set

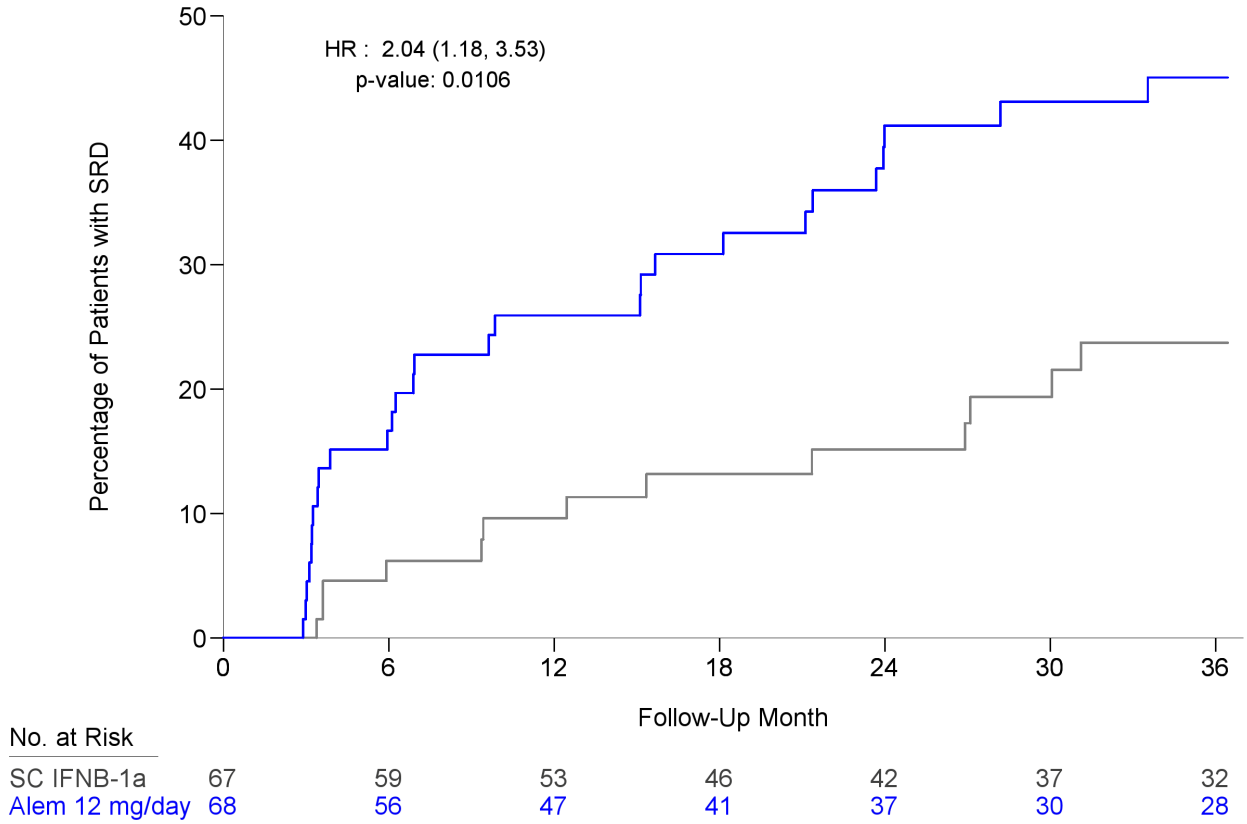


EDSS change from baseline estimated via mixed model for repeated measures with visit, treatment group, visit-by-treatment group interaction, country and baseline EDSS as covariates and unstructured covariance matrix

Sustained Reduction in Disability

Alemtuzumab-treated patients were more than twice as likely to experience SRD than patients treated with Rebif (p=0.0106) (Figure 5).

Figure 5: Kaplan-Meier Estimate of Time to 6-Month SRD, Study CAMMS223 Full Analysis Set



4.1.2 Phase 3 Study CAMMS323

4.1.2.1 Patient Disposition

In Study CAMMS323, 581 patients were randomized. Among the 376 patients treated with alemtuzumab, 97.6% completed the study (Table 7).

Table 7: Patient Disposition, Study CAMMS323

	IFNB-1a N=195 N (%)	Alemtuzumab 12 mg/day N=386 N (%)
Randomized	195 (100)	386 (100)
Discontinued prior to Treatment	8 (4.1)	10 (2.6)
Treated	187 (95.9)	376 (97.4)
Completed	173 (88.7)	367 (95.1)

Table 7: Patient Disposition, Study CAMMS323

	IFNB-1a N=195 N (%)	Alemtuzumab 12 mg/day N=386 N (%)
Discontinued study treatment	23 (12.3)	8 (2.1)
Discontinued from study	14 (7.2)	9 (2.3)
Lack of efficacy	2 (1.0)	0
Adverse event	5 (2.6)	0
Withdrew consent	5 (2.6)	4 (1.0)
Investigator decision	1 (0.5)	2 (0.5)
Pregnancy	1 (0.5)	0
Protocol violation	0	0
Lost to follow up	0	1 (0.3)
Other	0	1 (0.3)
Death	0	1 (0.3)

Percentages based on randomized patients except for discontinued study treatment which is based on the number of treated patients.

4.1.2.2 Baseline Demographic and MS Disease Characteristics

Baseline demographic and MS disease characteristics were well balanced across treatment groups and indicative of a treatment-naïve population with early, active RRMS (Table 8).

Table 8: Baseline Demographic and MS Disease Characteristics, Study CAMMS323 Full Analysis Set

Variable	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Age (years)		
Mean (SD)	33.2 (8.48)	33.0 (8.03)
Median	33.0	32.0
Min, Max	18.0, 53.0	18.0, 51.0
Sex, n (%)		
Male	65 (34.8)	133 (35.4)
Female	122 (65.2)	243 (64.6)
Race, n (%)		
White	180 (96.3)	352 (93.6)
MS History (time since first episode, years)		
Mean (SD)	2.0 (1.32)	2.1 (1.36)
Median	1.5	1.7
No. of relapses in prior 2 years, n (%)		
0	0	0
1	3 (1.6)	12 (3.2)
2	118 (63.1)	215 (57.2)
≥ 3	66 (35.3)	149 (39.6)
Baseline EDSS		
Mean (SD)	2.0 (0.79)	2.0 (0.81)
Median	2.0	2.0
Min, Max	0.0, 3.5	0.0, 4.0
Patients with gadolinium-enhancing lesions at baseline, n (%)	94 (51.4)	171 (46.1)

4.1.2.3 Maintenance of Rater Blinding

The integrity of rater blinding during the course of this study was assessed via worksheets on which the raters indicated for each assessment performed, whether they were blinded to the patient's treatment assignment (see Section 3.3.3). Overall, few patients had EDSS assessments performed by an unblinded rater (Table 9) and there was no apparent impact of unblinded assessments on the relapse or time to SAD results (see sensitivity analyses in Section 4.1.2.5). Most unblinding assessment involved EDSS performed by the treating neurologist at an

unscheduled relapse assessment. This practice was permissible until protocol Amendment 5 in 2010 and although it did not involve a breaking of study blind for the EDSS rater, such events were included in the analyses of unblinding since it involved an EDSS evaluation performed by a study physician with knowledge of treatment assignment.

Table 9: EDSS Blinded Rater Survey: CAMMS323 Full Analysis Set

Statistic	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Quarterly Scheduled EDSS Assessments		
Patients with blinded rater summary completed, n	187	376
Patients with at least one unblinded rater assessment, n (%)	3 (1.6)	1 (0.3)
Quarterly EDSS assessments performed, n	1613	3351
Unblinded EDSS assessments, n (%)	4 (0.2)	2 (0.1)
Unscheduled EDSS Assessments for Relapse		
Patients with blinded rater summary completed, n	187	376
Patients with at least one unblinded rater assessment, n (%)	5 (2.7)	6 (1.6)
Unscheduled EDSS assessments for relapse performed, n	118	111
Unblinded EDSS assessments, n (%)	6 (5.1)	9 (8.1)
Quarterly and Unscheduled EDSS Assessments		
Patients with blinded rater summary completed, n	187	376
Patients with at least one unblinded rater assessment, n (%)	8 (4.3)	7 (1.9)
Quarterly and unscheduled EDSS assessments performed, n	1731	3462
Unblinded EDSS assessments, n (%)	10 (0.6)	11 (0.3)

4.1.2.4 Relapse

Primary Endpoint: Relapse Rate

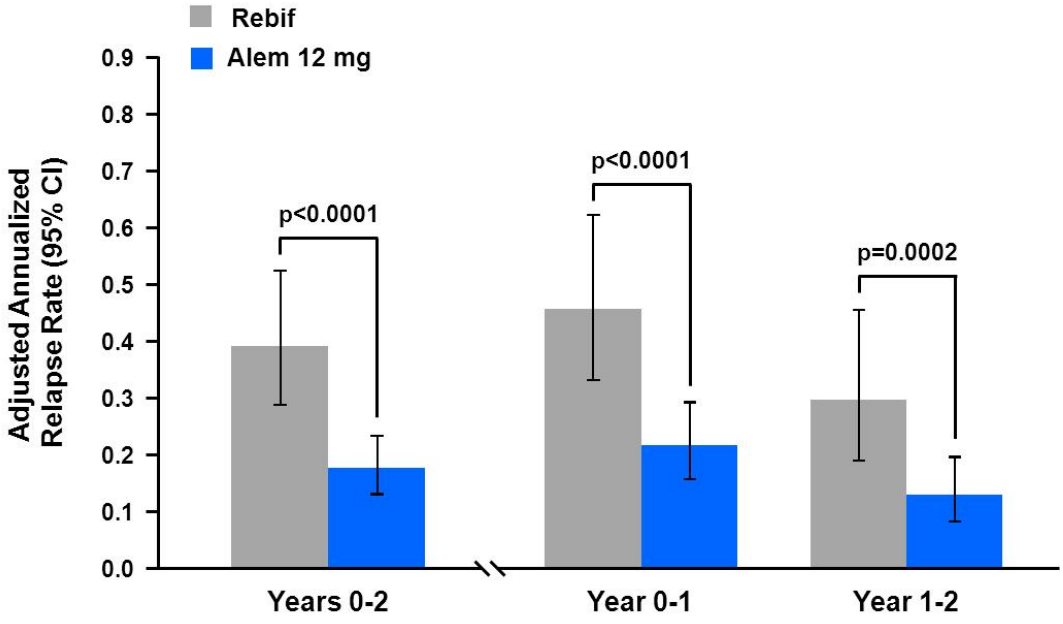
In CAMMS323, alemtuzumab 12 mg/day treatment resulted in a 55% reduction in relapse rate compared with Rebif ($p< 0.0001$) through 2 years (Table 10 and Figure 6), meeting the study's pre-specified success criteria.

Table 10: Relapse Rate and Treatment Effect Summary (2 Year Follow up), Study CAMMS323 Full Analysis Set

Statistic	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Patients with event, n	75	82
Total number of events	122	119
ARR (95% CI)	0.39 (0.29, 0.53)	0.18 (0.13, 0.23)
Rate ratio (95% CI)	--	0.45 (0.32, 0.63)
Treatment effect	--	55%
p-value	--	<0.0001

Rate ratio and p-value calculated using Anderson-Gill model with treatment group and geographic region as covariates and empirical variance estimation. ARR estimated by negative binomial regression with treatment group and geographic region as covariates, log of study follow-up time as an offset and empirical variance estimation

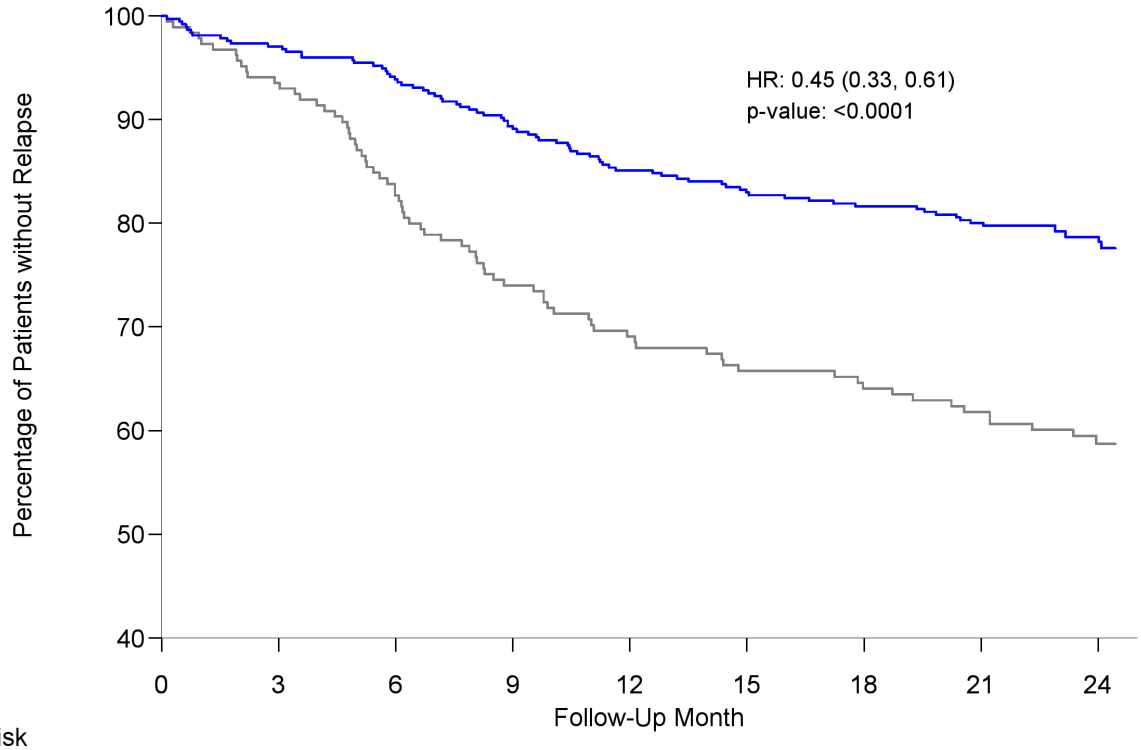
Figure 6: Annualized Relapse Rate (ARR), Study CAMMS323 Full Analysis Set



Other Relapse Endpoints

The percentage of patients who were relapse-free at Year 2 (secondary efficacy endpoint) was significantly higher for alemtuzumab-treated patients (78%) compared to Rebif treated patients (59%; $p < 0.0001$; Figure 7). The effects of alemtuzumab on relapses were supported by analyses demonstrating reductions in the rate of severe relapses by 61% (p=0.0056), and the rate of relapses treated with steroids by 58% ($p< 0.0001$).

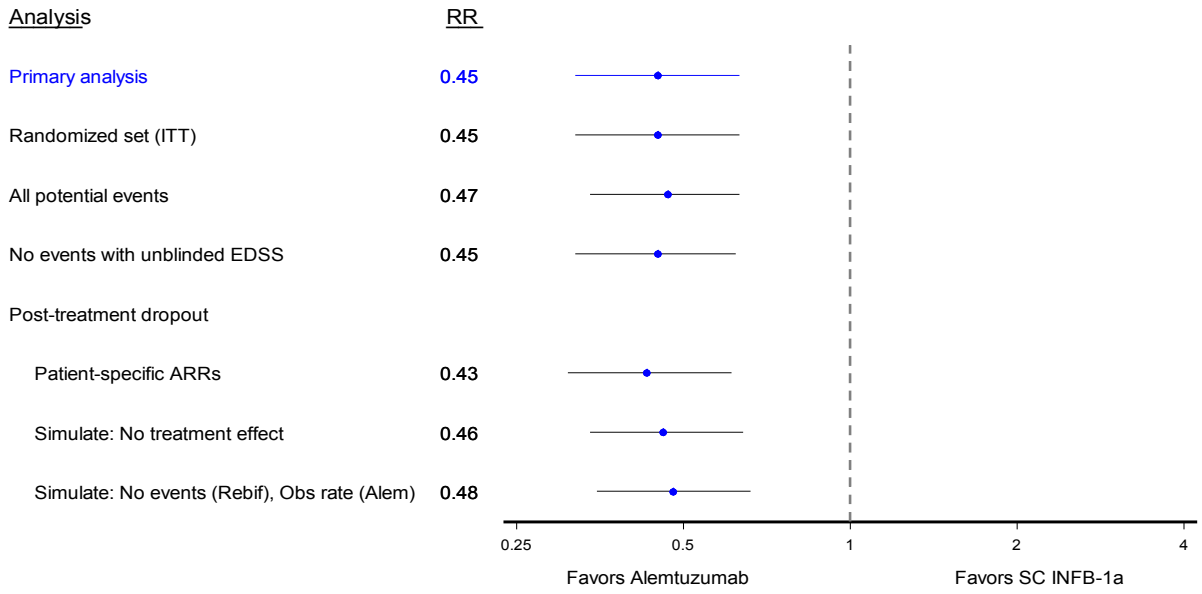
Figure 7: Kaplan-Meier Estimate of Time to First Relapse, Study CAMMS323 Full Analysis Set



No. at Risk									
SC IFNB-1a	187	175	156	137	127	118	116	109	101
Alem 12 mg/day	376	366	358	340	321	313	306	299	287

Sensitivity analyses assessing the influence of unblinded EDSS raters, patient dropout, and other factors demonstrated the robustness of study results (Figure 8). Analyses included using all suspected relapses (not restricted to RAP-confirmed events) and removing relapses associated with unblinded EDSS raters (Table 9). The influence of patient dropout was assessed by simulating relapses using patient-specific estimates of the annualized relapse rate from the available follow-up and, more conservatively, relapses assuming no treatment effect and, separately, no relapses for the missing follow-up of Rebif patients but the observed alemtuzumab relapse rate for alemtuzumab patients.

Figure 8: Relapse Rate Sensitivity Analyses, Study CAMMS323



4.1.2.5 Disability

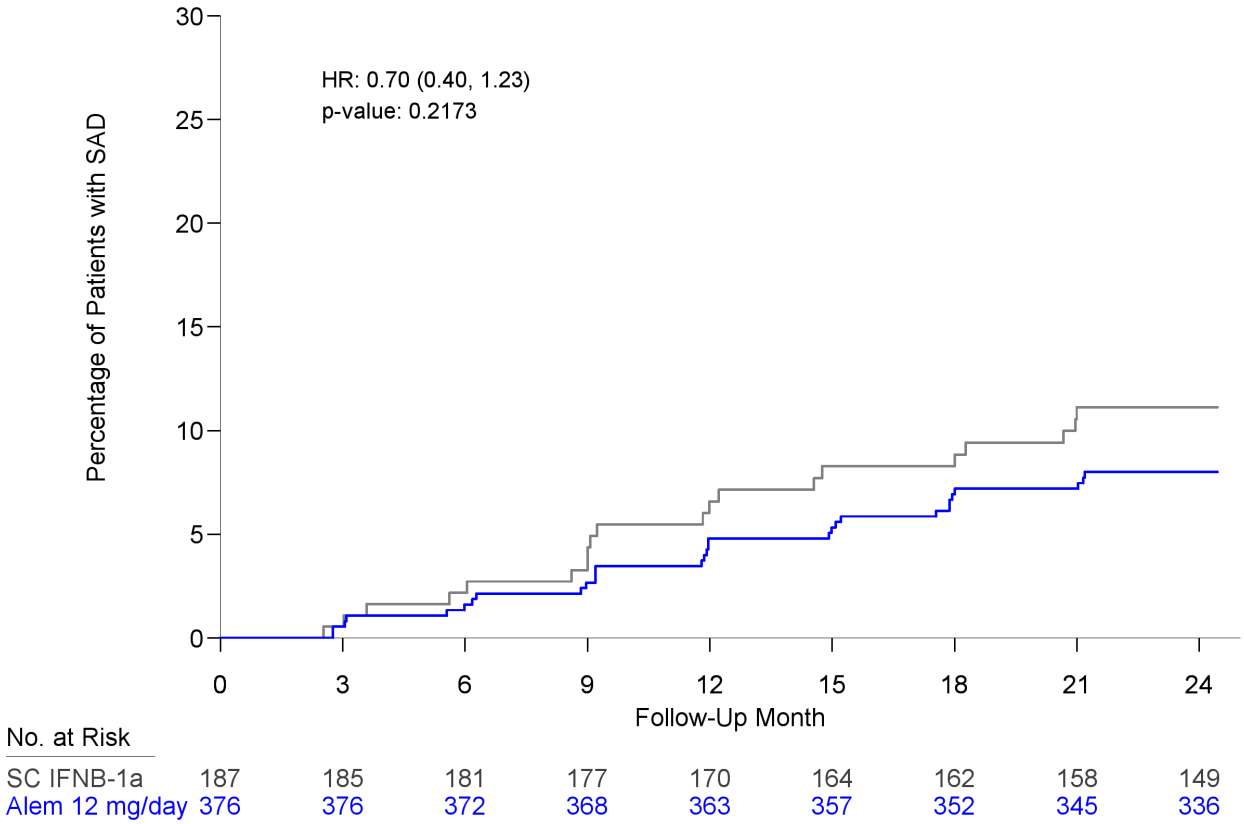
Primary Endpoint: Time to 6-month SAD

During 2 years of follow-up, 8.0% of alemtuzumab-treated patients and 11.1% of Rebif treated patients experienced 6-month SAD (Table 11 and Figure 9). The estimated treatment effect of 30% was not statistically significant (p=0.2173). The lower number of patients reaching SAD in the Rebif group (11.1% as opposed to 20% predicted in the study power assumptions) reduced the ability to detect a significant alemtuzumab treatment effect on time to SAD.

Table 11: Time to 6-Month SAD and Treatment Effect (2 Year Follow-Up), Study CAMMS323 Full Analysis Set

Statistic	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Proportion of patients with SAD (95% CI)	0.11 (0.07, 0.17)	0.08 (0.06, 0.11)
Hazard ratio (95% CI)	--	0.70 (0.40, 1.23)
Treatment effect	--	30%
p-value	--	0.2173

Figure 9: Kaplan Meier Estimate of Time to 6-Month SAD, Study CAMMS323 Full Analysis Set



Sensitivity analyses were conducted to assess the influence of unblinded EDSS raters, patient dropout, and other factors on the primary time to SAD results; none of the factors influenced the outcome or conclusions.

Other Disability Endpoints

The lack of EDSS progression in the Rebif group also impacted analyses of other EDSS-related endpoints. The EDSS change from baseline (secondary endpoint) was -0.14 for alemtuzumab-treated patients and -0.14 of IFNB-1a-treated patients (p=0.4188).

MSFC

Alemtuzumab-treated patients had significantly larger increases from baseline in MSFC scores than Rebif-treated patients (p=0.0115; Table 12). Further, alemtuzumab, but not Rebif -treated patients, experienced significant improvement from Baseline in MSFC scores over the 2-year study period, indicating improved function (or decreased disability) with treatment.

Table 12: MSFC Z-Score Change from Baseline to Year 2, Study CAMMS323 Full Analysis Set

Measurement	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Overall[a] p-value		0.0115
Change from baseline[b] (95% CI) p-value	0.05 (-0.02, 0.13) 0.1596	0.12 (0.06, 0.18) < 0.0001

[a].Wei-Lachin (multivariate, non-parametric test)
[b] MSFC change from baseline estimated via mixed model for repeated measures with visit, treatment group, visit-by-treatment group interaction, geographic region and baseline MSFC as covariates and unstructured covariance matrix

4.1.2.6 Imaging

T2-hyperintense lesion volume reflects the inflammatory demyelination and edema characteristic of active MS lesions, as well as the sclerotic gliosis of end-stage MS plaques. T2 lesion volume change was a secondary endpoint in this study. During the first year of study, given that the treatment-naïve population in CAMMS323 had never previously received therapy with any DMT, both treatment groups experienced marked reductions in lesion volume upon exposure to effective therapy, likely representing some degree of resolution of acute inflammation and edema as well as prevention of new lesion formation. Consequently, there was no difference between groups in the first year of the study leading to no significant difference overall. However, a difference between the groups became apparent during the second year (Month 12 to Month 24) of the study (p=0.0364) with alemtuzumab-treated patients exhibiting a significantly greater reduction in T2-hyperintense lesion volume than Rebif treated patients, likely reflecting an effect of alemtuzumab on the formation of new T2-hyperintense lesions. This conclusion is supported by the finding that, over the 2-year duration of follow up, alemtuzumab significantly reduced the risk of developing new or enlarging T2 hyperintense lesions by 34% (p=0.0352) as well as the risk of Gd-enhancing lesions by 70% (p<0.0001), and new T1 hypointense lesions by 34% (p=0.0545), with the most pronounced risk reductions during Year 2 (Table 13).

In addition, alemtuzumab significantly reduced the rate of brain atrophy over the 2-year study period as measured by BPF with a median percent change from baseline in BPF of 0.867 in the alemtuzumab group compared with 1.488 in the Rebif group (p<0.0001), representing a 42% slowing of atrophy relative to Rebif treated patients.

Table 13: Summary of MRI Outcomes, Study CAMMS323 Full Analysis Set

MRI variable	IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)	p-value
Median change in volume of T2-hyperintense lesions over 24 months (Q1, Q3) [a]	–6.5% (–20.7 to 2.5)	–9.3% (–19.6 to –0.2)	0.3080
Patients with new or enlarging T2-hyperintense lesions over 24 months [b]	99/172 (58%)	176/363 (48%)	0.0352
Patients with gadolinium-enhancing lesions at 24 months [b]	34/178 (19%)	26/366 (7%)	<0.0001
Patients with new T1-hypointense lesions over 24 months [b]	54/172 (31%)	87/363 (24%)	0.0545
Median change in brain parenchymal fraction over 24 months (Q1, Q3) [a]	–1.488% (–2.355 to –0.567)	–0.867% (–1.470 to –0.254)	<0.0001

[a] P-value from ranked ANCOVA with adjustment for geographic region and baseline measure.
[b] P-value from logistic regression model with treatment group and baseline lesion count (for gadolinium-enhancing lesions) or baseline lesion volume (for T2-hyperintense and T1-hypointense lesions) as covariates.

4.1.3 Phase 3 Study CAMMS324

Results for Study CAMMS324 presented in the following section include those for the alemtuzumab 12 mg and Rebif arms. Efficacy results for the 24 mg arm are not presented since this arm was closed to enrollment following Amendment 2 (see Section 3.4.1) and its efficacy results were considered exploratory. A brief summary of the efficacy data in the 24 mg dose group is provided along with a rationale for selection of the 12 mg dose as the proposed commercial dose in Appendix E, Section 10.5.

4.1.3.1 Patient Disposition

In Study CAMMS324, 840 patients were randomized and 798 received treatment (Table 14). Among the 798 patients treated in the study, 86.6% (175/202) of the Rebif-treated patients, 97.7% (416/426) of the alemtuzumab 12 mg/day-treated patients, and 96.5% (164/170) of the alemtuzumab 24 mg/day-treated patients completed the study. Ninety-three percent of patients treated with alemtuzumab 12/mg completed 2 full cycles of treatment.

The patients who withdrew after randomization but before treatment primarily left the study because they did not want to receive the allocated treatment; these patients were not included in the primary efficacy analysis but the influence of dropouts on the primary efficacy results was explored in sensitivity analyses and found to be minimal (see Figure 12 and Figure 14).

Table 14: Patient Disposition, Study CAMMS324

	IFNB-1a N=231 N (%)	Alemtuzumab 12 mg/day N=436 N (%)	Alemtuzumab 24 mg/day N=173 N (%)
Randomized	231	436	173
Discontinued prior to Treatment	29 (12.6)	10 (2.3)	3 (1.7)
Treated	202 (87.4)	426 (97.7)	170 (98.3)
Completed	175 (75.8)	416 (95.4)	164 (94.8)
Discontinued study treatment	44 (21.8)	22 (5.1)	9 (5.2)
Discontinued from study	27 (11.7)	10 (2.3)	6 (3.5)
Adverse event	6 (2.6)	1 (0.2)	0
Lack of efficacy	6 (2.6)	0	0
Investigator decision	3 (1.3)	2 (0.5)	0
Withdrew consent	9 (3.9)	4 (0.9)	3 (1.7)
Lost to follow up	1 (0.4)	1 (0.2)	2 (1.2)
Protocol violation	0	0	0
Pregnancy	1 (0.4)	0	0
Death	0	1 (0.2)	1 (0.6)
Other	1 (0.4)	1 (0.2)	0

Percentages based on randomized patients except for discontinued study treatment which is based on the number of treated patients.

4.1.3.2 Baseline Demographic and MS Disease Characteristics

Demographic and baseline disease characteristics for the patients in Study CAMMS324 were well balanced across treatment groups (Table 15 and Table 16). Compared with patients in the treatment naïve studies, the average CAMMS324 patient was older, had longer MS duration, and

had more disability at Baseline. Further, patients had received prior therapy with beta interferon or glatiramer acetate for a mean of 3 years prior to enrollment, and roughly one-third of all patients were treated with more than one disease modifying therapy.

Table 15: Baseline Demographic and MS Disease Characteristics, Study CAMMS324 Full Analysis Set

Variable	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Age (years)		
Mean (SD)	35.8 (8.77)	34.8 (8.36)
Median	35.0	34.0
Min, Max	18.0, 54.0	18.0, 55.0
Sex, n (%)		
Male	71 (35.1)	145 (34.0)
Female	131 (64.9)	281 (66.0)
Race, n (%)		
White	187 (92.6)	385 (90.4)
MS History (time since first episode, years)		
Mean (SD)	4.7 (2.86)	4.5 (2.68)
Median	4.1	3.8
Number of relapses in the preceding 2 Years, n (%)		
0	0	0
1	7 (3.5)	15 (3.5)
2	109 (54.0)	215 (50.5)
≥ 3	86 (42.6)	196 (46.0)
Baseline EDSS		
Mean (SD)	2.7 (1.21)	2.7 (1.26)
Median	2.5	2.5
Min, Max	0.0, 6.0	0.0, 6.5
Patients with gadolinium-enhancing lesions at baseline, n (%)	87 (43.7)	178 (42.4)

Table 16: Prior MS Disease Modifying Treatment History, Study CAMMS324 Full Analysis Set

Variable	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Duration of MS therapy (months)		
Mean (SD)	36 (23.7)	35 (25.0)
Number of MS therapies used, %		
1	74.8	70.2
2	20.2	21.6
≥ 3	5.0	8.2
Prior MS Therapy, %	100	100
Interferon beta-1a	53.5	54.5
IM (Avonex)	22.8	28.2
SC (Rebif 22 or 44 μg)	36.1	34.3
Interferon beta-1b (Betaseron)	31.2	36.2
Glatiramer acetate	34.2	34.3
Other	6.9	6.8

4.1.3.3 Maintenance of Rater Blinding

The integrity of rater blinding during the course of this study was assessed via worksheets on which the raters indicated, for each assessment they performed, whether they were blinded to each patient's treatment assignment (Section 3.3.3). Overall, few patients had EDSS assessments performed by an unblinded rater (Table 17). All unblinded assessments at unscheduled visits were conducted by the treating neurologist before the implementation of Protocol Amendment 4 in 2010, as up until that time the protocol allowed the treating neurologist to perform unscheduled EDSS assessments in the event the blinded rater was not available. Although these events did not involve a breaking of study blind for the EDSS rater, they were included in the analysis of unblinding since they involved an EDSS evaluation performed by a study physician with knowledge of treatment assignment.

The small number of patients with EDSS assessments performed by an unblinded rater had no impact on the relapse or time to SAD results, as shown in sensitivity analyses (Section 4.1.3.5).

Table 17: EDSS Blinded Rater Survey; CAMMS324 Full Analysis Set

Statistic	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Quarterly Scheduled EDSS Assessments		
Patients with blinded rater summary completed, n	201	426
Patients with at least one unblinded rater assessment, n (%)	2 (1.0)	2 (0.5)
Quarterly EDSS assessments performed, n	1676	3756
Unblinded EDSS assessments, n (%)	2 (0.1)	3 (0.1)
Unscheduled EDSS Assessments for Relapse		
Patients with blinded rater summary completed, n	201	426
Patients with at least one unblinded rater assessment, n (%)	6 (3.0)	4 (0.9)
Unscheduled EDSS assessments for relapse performed, n	202	231
Unblinded EDSS assessments, n (%)	6 (3.0)	4 (1.7)
Quarterly and Unscheduled EDSS Assessments		
Patients with blinded rater summary completed, n	201	426
Patients with at least one unblinded rater assessment, n (%)	7 (3.5)	5 (1.2)
Quarterly and unscheduled EDSS assessments performed, n	1878	3987
Unblinded EDSS assessments, n (%)	8 (0.4)[a]	7 (0.2)

4.1.3.4 Relapse

Primary Endpoint: Relapse Rate

In Phase 3 Study CAMMS324, alemtuzumab significantly reduced the relapse rate through 2 years by 49% compared with Rebif ($p < 0.0001$; Table 18 and Figure 10), meeting the study's pre-specified success criteria.

Table 18: Relapse Rate and Treatment Effect Summary (2 Year Follow-Up), Study CAMMS324 Full Analysis Set

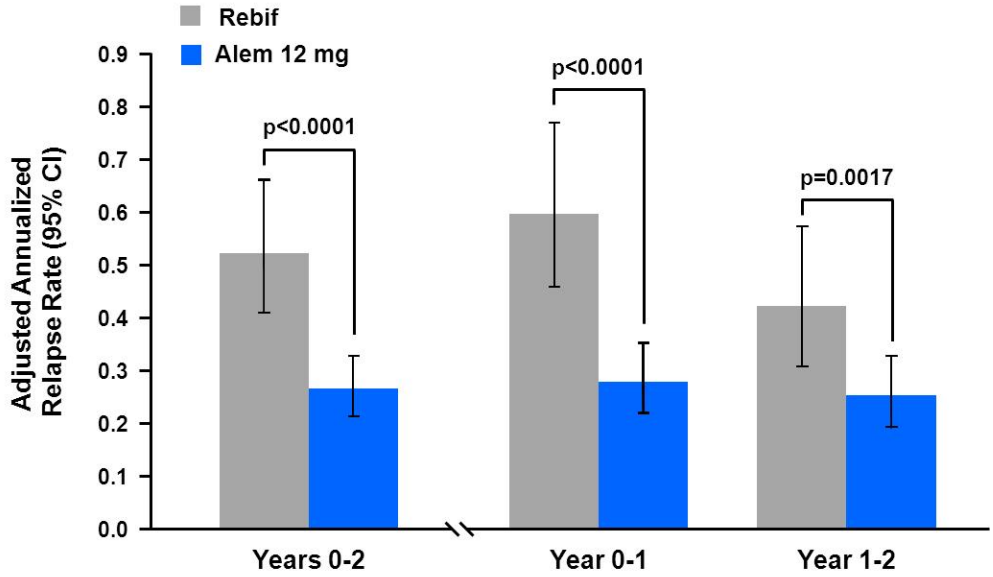
Statistic	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Patients with events, n	104	147
Total number of events	201	236
ARR (95% CI)	0.52 (0.41, 0.66)	0.26 (0.21, 0.33)
Rate ratio (95% CI)	--	0.51 (0.39, 0.65)
Treatment effect	--	49%
p-value	--	<0.0001

Table 18: Relapse Rate and Treatment Effect Summary (2 Year Follow-Up), Study CAMMS324 Full Analysis Set

Statistic	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)

Rate ratio and p-value calculated using Anderson-Gill model with treatment group and geographic region as covariates and empirical variance estimation. ARR estimated by negative binomial regression with treatment group and geographic region as covariates, log of study follow-up time as an offset and empirical variance estimation.

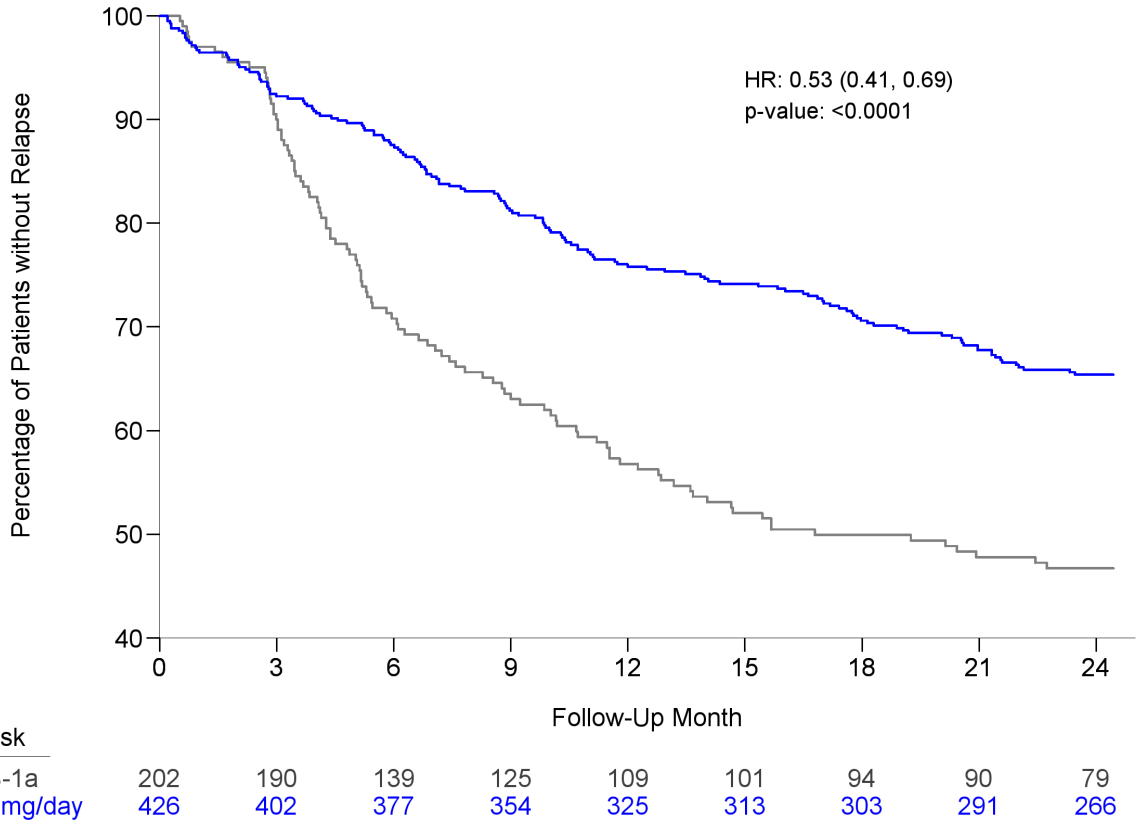
Figure 10: Annualized Relapse Rate, Study CAMMS324 Full Analysis Set



Other Relapse Endpoints

The percentage of patients who were relapse-free at Year 2 (secondary efficacy endpoint) was significantly higher for alemtuzumab-treated patients (65.4%) compared to Rebif-treated patients (46.7%; $p < 0.0001$;Figure 11). The robust effects of alemtuzumab on relapses were confirmed through supportive analyses demonstrating reductions in the rate of severe relapses by 48% ($p=0.0121$), the rate of relapses treated with steroids by 56% ($p< 0.0001$) and the rate of relapses that led to hospitalization by 55% ($p = 0.0045$).

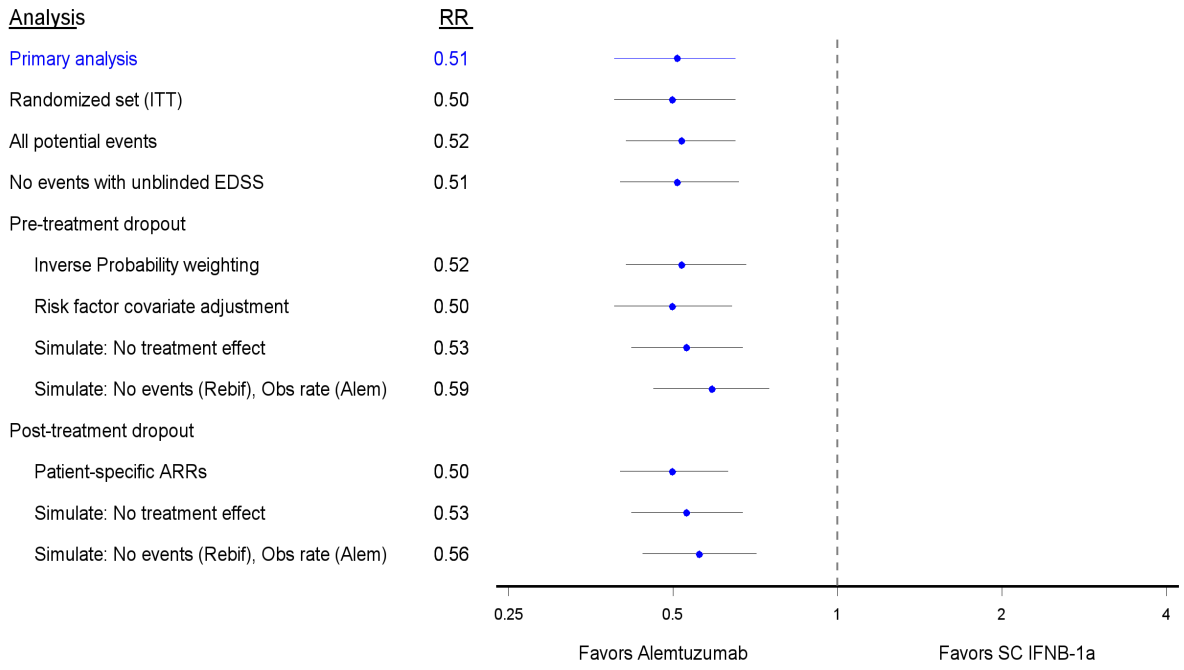
Figure 11: Kaplan-Meier Estimate of Time to First Relapse, Study CAMMS323 Full Analysis Set



No. at Risk									
SC IFNB-1a	202	190	139	125	109	101	94	90	79
Alem 12 mg/day	426	402	377	354	325	313	303	291	266

Sensitivity analyses assessing the influence of unblinded EDSS raters, pre- and post-treatment patient dropout, and other factors demonstrated the robustness of study results (Figure 12). Analyses included using all suspected relapses (not restricted to RAP-confirmed events) and removing relapses associated with unblinded EDSS raters. Importantly, the sensitivity analyses using inverse probability weighting indicate that pre-treatment dropout does not appear to have biased the relapse results. Inverse probability weighting accounts for pre-treatment dropout by re-weighting the observed data to simulate what the results would have been had the pre-treatment dropouts actually completed follow-up. Other analyses addressing pre-treatment drop out conservatively simulated data assuming no treatment effect and, separately, assuming no relapses for the pre-treatment dropouts randomized to Rebif but the observed alemtuzumab relapse rate for the pre-treatment dropouts randomized to alemtuzumab. Similar results are seen from the analyses focused on post-treatment dropout.

Figure 12: Relapse Rate Sensitivity Analyses, Study CAMMS324



4.1.3.5 Disability

Primary Endpoint: Time to 6-month SAD

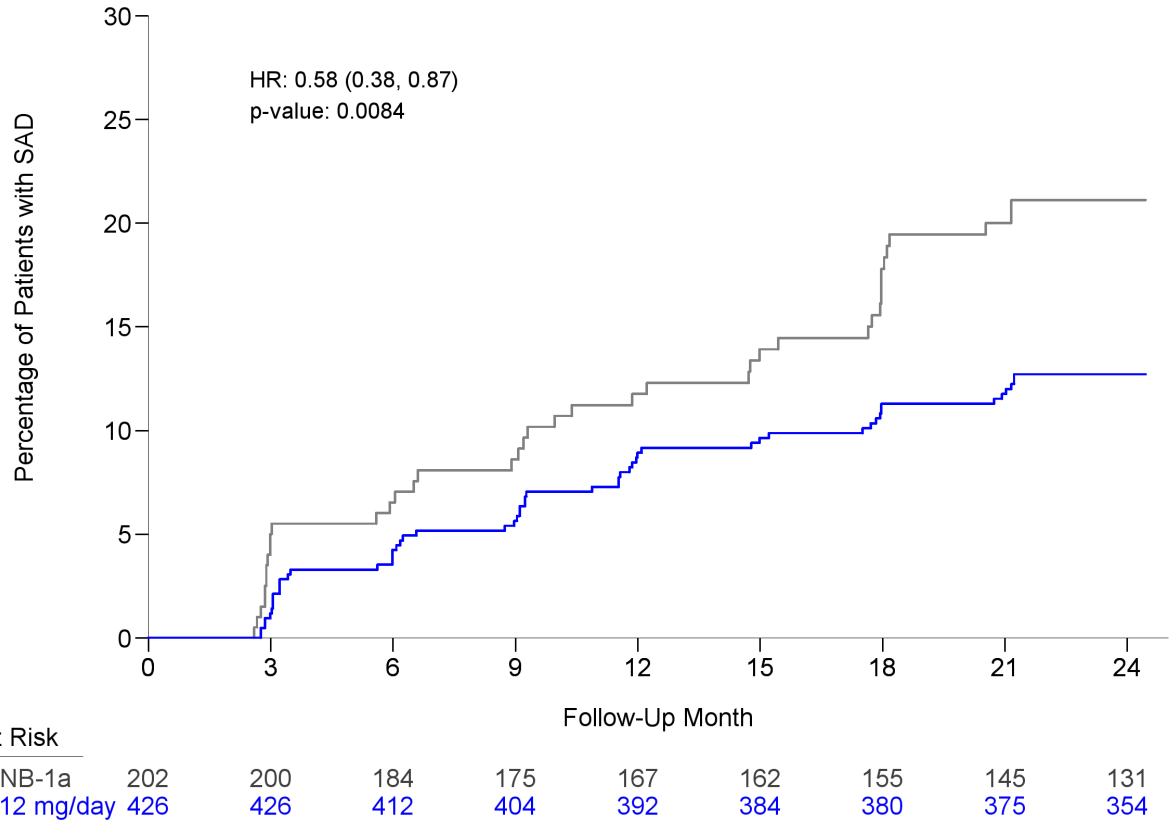
Alemtuzumab significantly reduced the risk of SAD through 2 years by 42% compared with Rebif (p= 0.0084). The percentage of patients experiencing SAD at 2 years was 12.7% in the alemtuzumab group and 21.1% in the Rebif group (Table 19 and Figure 13).

Table 19: Time to 6-Month SAD and Treatment Effect (2 Year Follow-Up), Study CAMMS324 Full Analysis Set

Statistic	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Proportion of patients with SAD (95% CI)	0.21 (0.16, 0.28)	0.13 (0.09, 0.16)
Hazard ratio (95% CI)	--	0.58 (0.38, 0.87)
Treatment effect	--	42%
p-value	--	0.0084

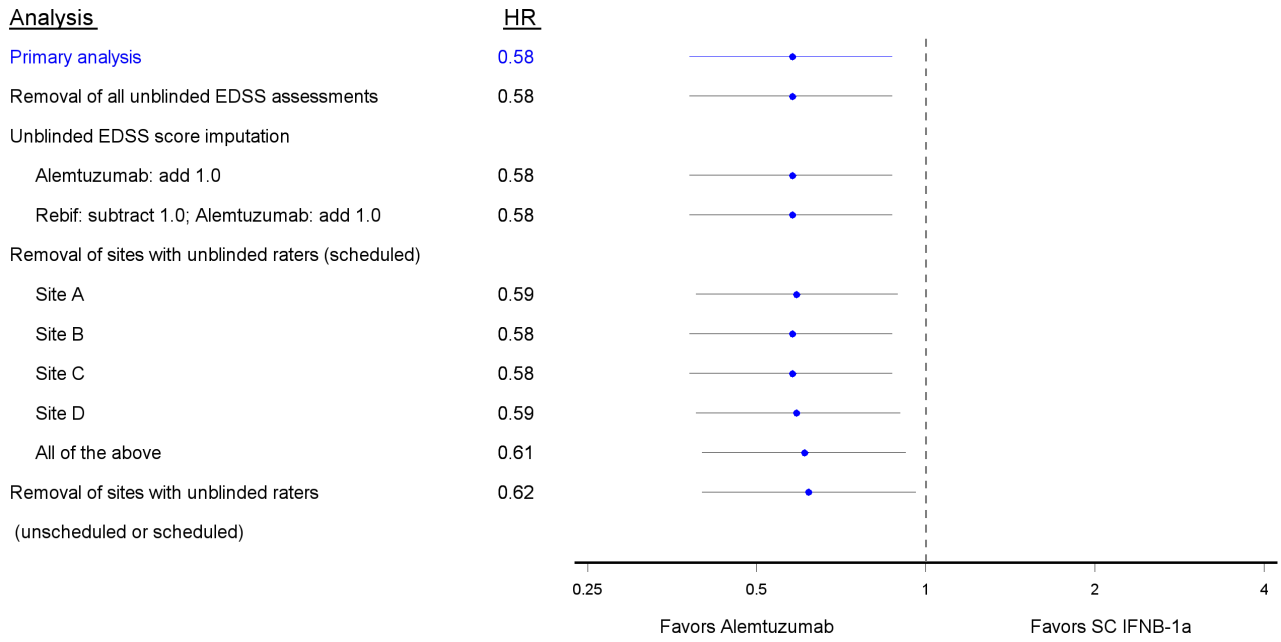
Hazard ratio and p-value calculated from proportional hazards model with treatment group and geographic region as covariates and empirical variance estimation. Proportion of patients experiencing SAD estimated via Kaplan-Meier method.

Figure 13: Kaplan Meier Estimate of Time to 6-Month SAD, Study CAMMS324 Full Analysis Set



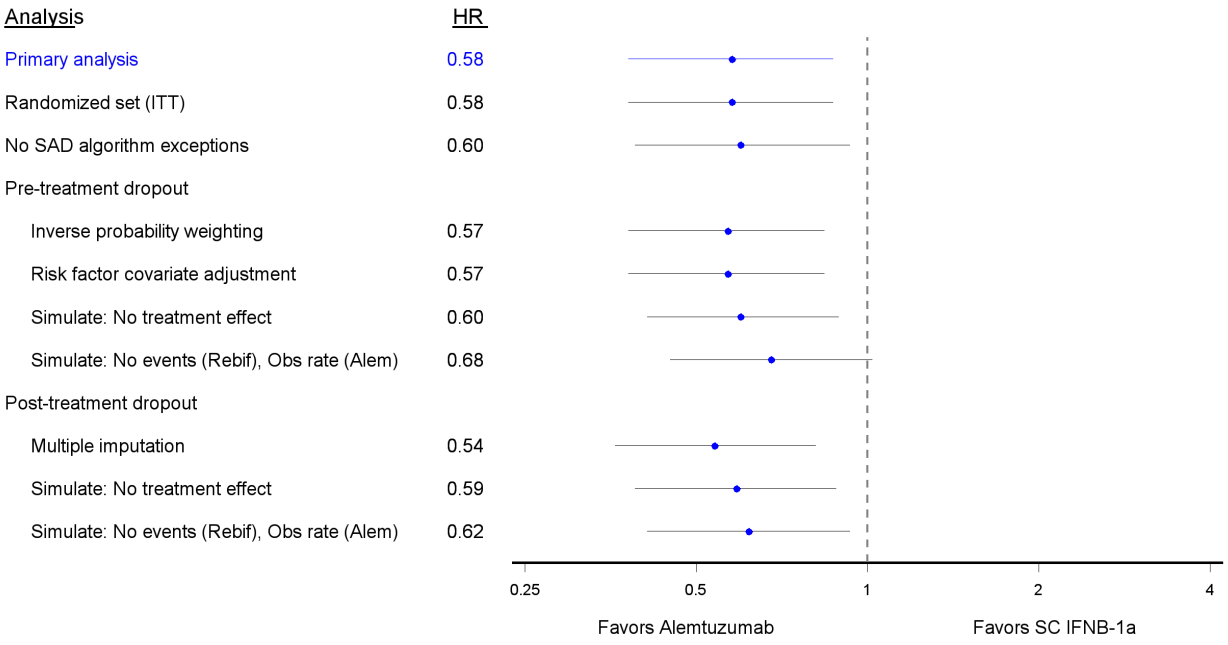
Sensitivity analyses assessing the influence of unblinded EDSS raters, pre- and post-treatment patient dropout, and other factors on the primary time to SAD results demonstrated robustness of study results. The sensitivity analysis results addressing unblinded EDSS assessments (Table 17) are presented in Figure 14. The sensitivity analyses included removing EDSS assessments associated with unblinded raters and replacing unblinded EDSS scores with the most recent blinded EDSS plus/minus some increment assuming unblinded rater bias. Additionally, the primary efficacy model was rerun after removal of sites that reported an unblinded quarterly EDSS assessment. Another sensitivity analysis removed all sites with a reported unblinded quarterly EDSS assessment or a reported unblinded unscheduled EDSS assessment. These analyses indicate that the primary time to SAD result was not influenced by unblinded EDSS assessments.

Figure 14: Time to 6-Month SAD Sensitivity Analyses Pertaining to Unblinded EDSS Raters, Study CAMMS324



As with the relapse rate, the sensitivity analyses using inverse probability weighting and simulation of SAD data for the pre-treatment dropouts assuming no treatment effect and, separately, assuming no SAD for the pre-treatment dropouts randomized to Rebif but the observed alemtuzumab SAD incidence indicate that pre-treatment dropout does not appear to have biased the SAD results Figure 15. The conservative nature of the sensitivity analysis that assumes no SAD for the pre-treatment dropouts randomized to Rebif is shown by noting that the probability of this happening if the true 2-year incidence of SAD was 21.1% (the incidence for Rebif patients in the primary analysis; Table 19) is $(1\text{-}0.211)^{29} = 0.001$. Similar results are seen from the analyses focused on post-treatment dropout including an analysis using multiple imputation.

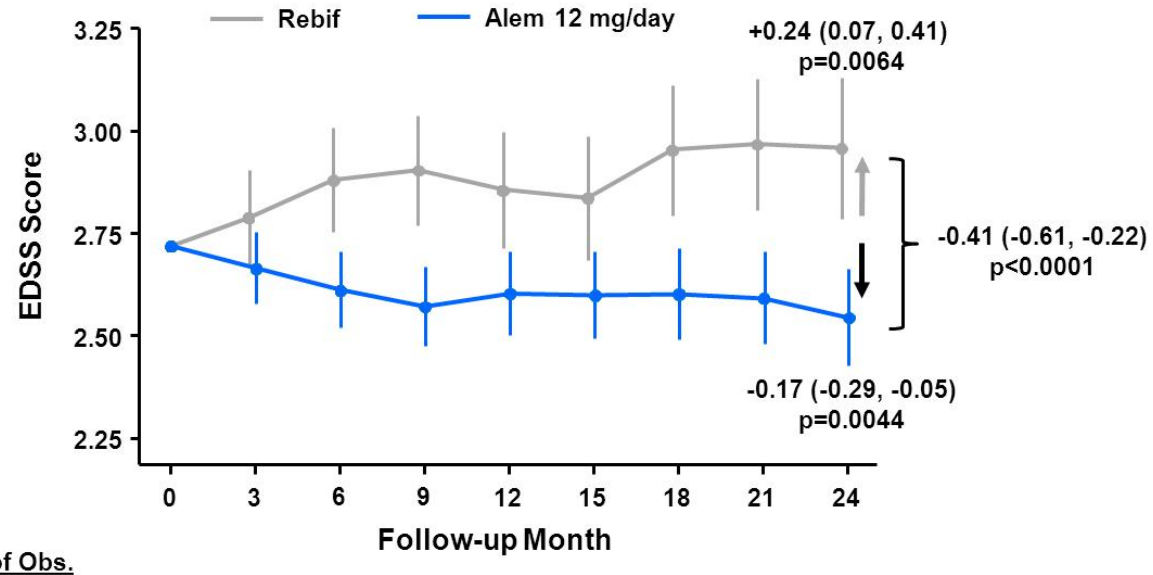
Figure 15: Time to 6-Month SAD Sensitivity Analyses, Study CAMMS324



Other Disability Endpoints

In the analysis of change from baseline in EDSS score, a secondary endpoint, alemtuzumab-treated patients experienced significant improvement from baseline in mean EDSS score (-0.17), whereas Rebif-treated patients experienced a significant worsening (0.24), and this group difference (0.41) was statistically significant ($p < 0.0001$). The difference in the mean EDSS scores was statistically significant by Month 6 ($p = 0.0003$), and this difference was maintained throughout the 2 year study period (Figure 16).

Figure 16: EDSS Change from Baseline, Study CAMMS324 Full Analysis Set

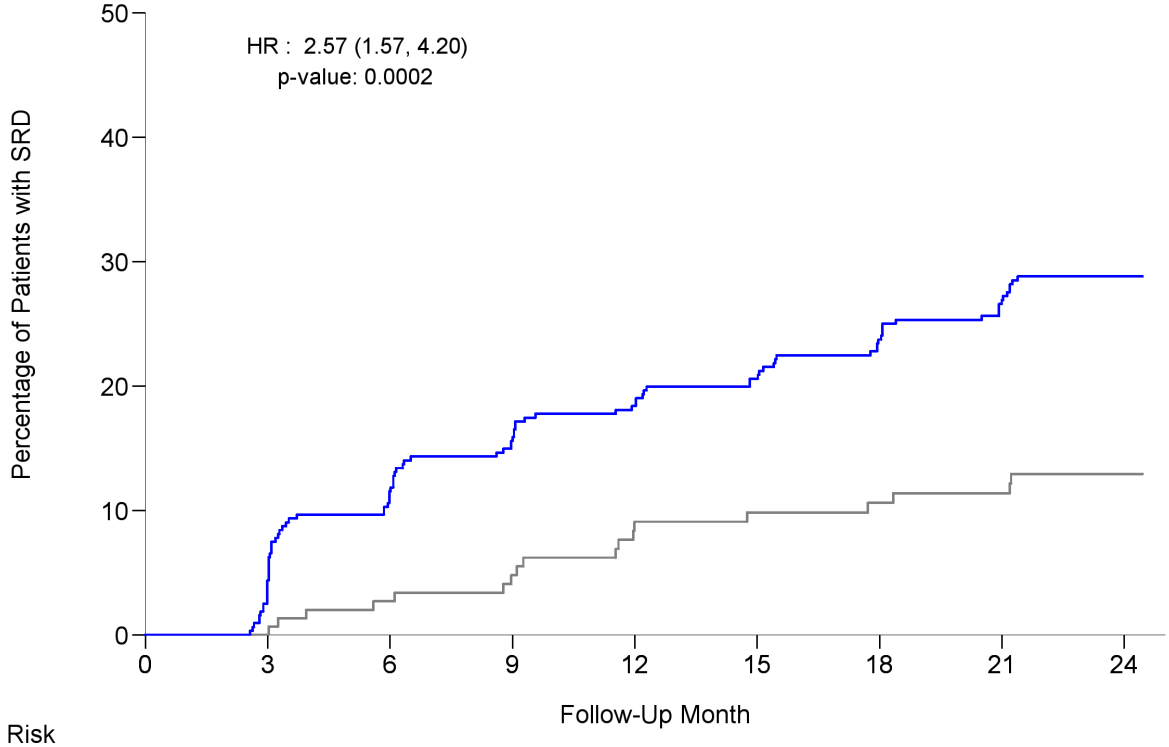


No. of Obs.									
Rebif	202	198	194	190	185	180	176	172	174
Alem 12 mg/day	426	419	419	419	422	415	410	413	413

EDSS change from baseline estimated via mixed model for repeated measures with visit, treatment group, visit-by-treatment group interaction, geographic region and baseline EDSS as covariates and unstructured covariance matrix

Change in disability was further explored by evaluating SRD. Alemtuzumab-treated patients were more than 2.5-times more likely to achieve SRD than Rebif treated patients (28.8% versus 12.9%, p=0.0002; Figure 17).

Figure 17: Kaplan-Meier Estimate of Time to 6-Month SRD, Study CAMMS324 Full Analysis Set



No. at Risk

SC IFNB-1a	153	151	142	137	129	122	117	114	107
Alem 12 mg/day	321	321	290	275	262	254	245	235	213

Consistent with the results of the EDSS change from baseline and the SRD assessments in the Phase 2 Study CAMMS223, these results provided additional evidence that alemtuzumab treatment not only reduces the risk of disease progression, but may also reduce pre-existing disability and improve neurological symptoms.

MSFC

Alemtuzumab-treated patients had significantly higher MSFC scores after treatment compared with Rebif-treated patients (p = 0.0022). Alemtuzumab-treated patients experienced significant improvement in MSFC scores at Year 2 (p = 0.0003), whereas Rebif patients did not (p = 0.2139; Table 20). Similarly, when the Sloan chart was combined with the MSFC to create a 4-dimensional composite that incorporates visual function (Balcer, 2000, Mult Scler), alemtuzumab-treated patients had significantly higher scores after treatment compared with Rebif-treated patients (p = 0.0018).

Table 20: MSFC Z-Score Change from Baseline to Year 2, Study CAMMS324 Full Analysis Set

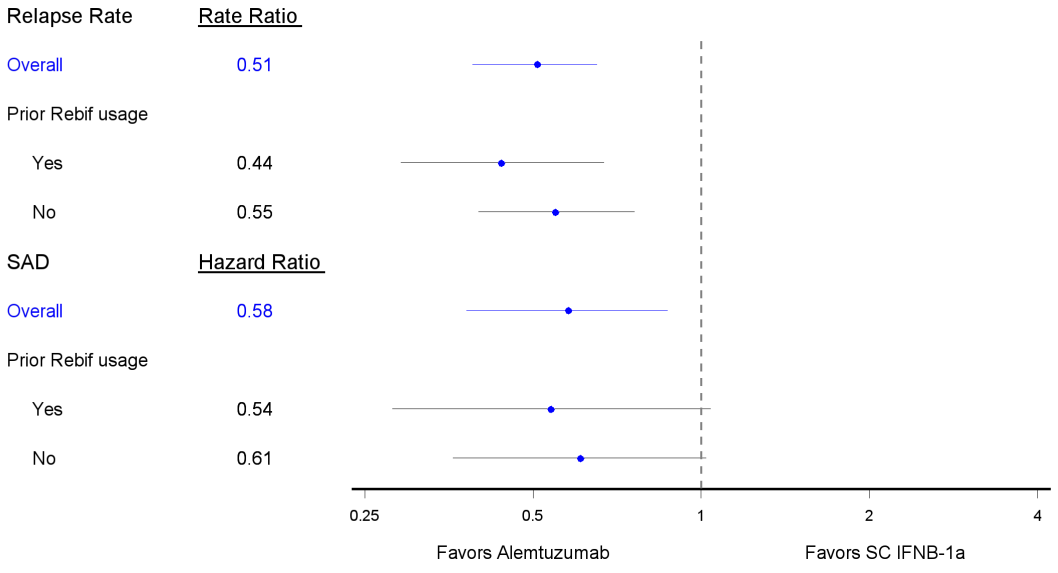
Measurement	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Overall[a] p-value		 0.0022
Change from baseline[b] (95% CI) p-value	-0.04 (-0.10, 0.02) 0.2139	0.08 (0.04, 0.12) 0.0003

[a] Wei-Lachin (multivariate, non-parametric test)
[b] MSFC change from baseline estimated via mixed model for repeated measures with visit, treatment group, visit-by-treatment group interaction, geographic region and baseline MSFC as covariates and unstructured covariance matrix

4.1.3.6 Efficacy by Prior DMT Use

Study eligibility criteria required that patients experience a relapse while on treatment with another DMT for MS. As shown in Table 16, 36% of patients in the Rebif group and 34% of patients in the alemtuzumab 12 mg group had received prior treatment with Rebif before enrolling in CAMMS324. Primary endpoint results were similar whether or not patients had a prior history of Rebif use Figure 18.

Figure 18: Primary Efficacy Results by Prior Use of Rebif, Study CAMMS324 Full Analysis Set



4.1.3.7 Imaging

Key MRI outcomes are shown in Table 21.

Table 21: Summary of MRI Outcomes, Study CAMMS324, Full Analysis Set

MRI variable	IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)	p-value
Median change in volume of T2-hyperintense lesions over 24 months (Q1, Q3) [a]	–1.23% (–11.13 to 11.39)	–1.27% (–12.70 to 7.78)	0.1371
Patients with new or enlarging T2-hyperintense lesions over 24 months [b]	127/187 (68%)	186/403 (46%)	<0.0001
Patients with gadolinium-enhancing lesions at 24 months [b]	44/190 (23%)	38/410 (9%)	<0.0001
Patients with new T1-hypointense lesions over 24 months [b]	71/187 (38%)	80/403 (20%)	<0.0001
Median change in brain parenchymal fraction over 24 months (Q1, Q3) [a]	–0.810% (–1.539 to 0.203)	–0.615% (–1.299 to 0.006)	0.0121

[a] P-value from ranked ANCOVA with adjustment for geographic region and baseline measure.
[b] P-value from logistic regression model with treatment group and baseline lesion count (for gadolinium-enhancing lesions) or baseline lesion volume (for T2-hyperintense and T1-hypointense lesions) as covariates.

Similar to CAMMS323, during the first year of study, both groups experienced a reduction (improvement) in T2 lesion volume compared with baseline leading to no significant difference in T2 lesion volume change between groups overall but, as in study CAMMS323, a difference between the groups became apparent during the second year of the study (p=0.0261) when the IFNB 1a treated group experienced a median increase in lesion volume while the alemtuzumab treated group remained stable. Further, as in CAMMS323, alemtuzumab significantly reduced the risk of developing new or enlarging T2 hyperintense lesions by 62% ($p < 0.0001$), as well as the risk of Gd-enhancing lesions by 69% ($p < 0.0001$), and new T1-hypointense lesions by 63% ($p<0.0001$), with the most pronounced risk reductions being observed during Year 2.

In addition, alemtuzumab significantly reduced the rate of brain atrophy over the 2-year study period as measured by BPF with a median percent change from baseline BPF of -0.615 in the

alemtuzumab group compared with -0.810 in the Rebif group (p=0.0121), representing a 24% slowing of atrophy relative to Rebif-treated patients.

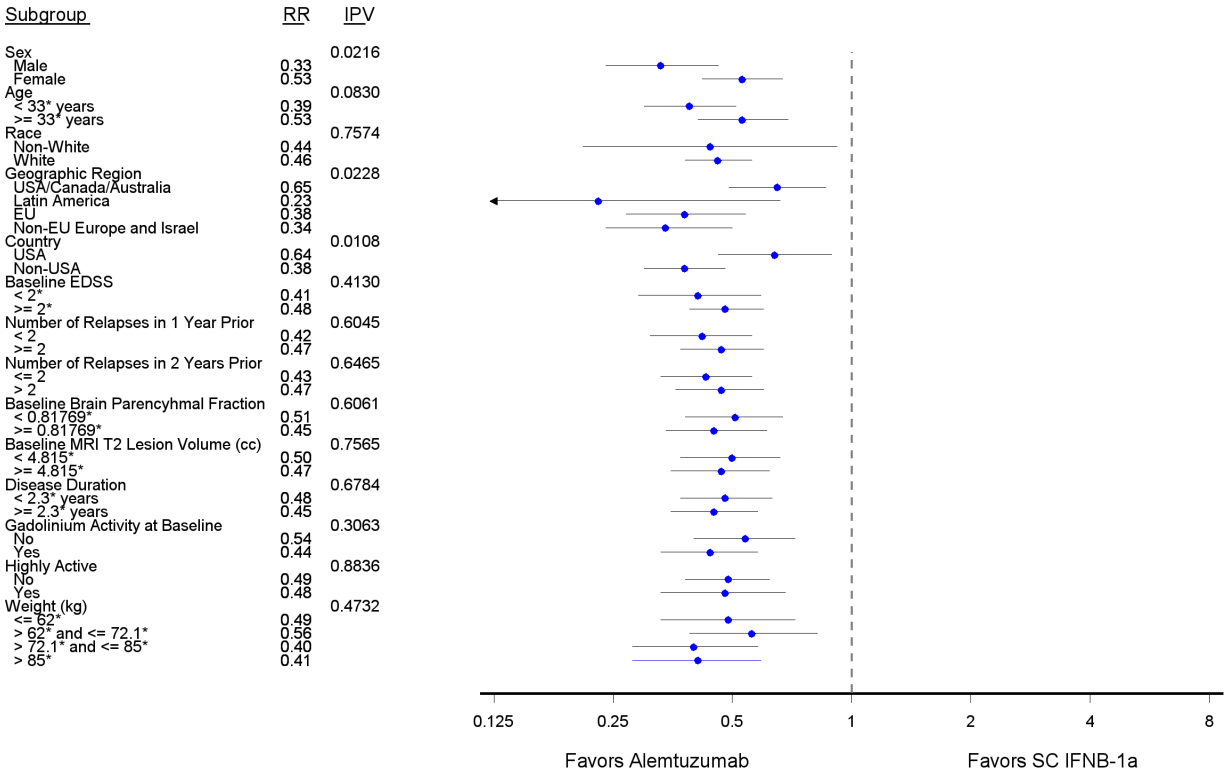
4.1.4 Subgroup Analyses

Analyses were performed to evaluate the consistency of the alemtuzumab treatment effect across predefined subgroups based on baseline demographic and disease characteristics. These subgroup analyses included the co-primary efficacy endpoints of relapse rate and time to 6-month SAD. Data from the 3 clinical studies were pooled for other subgroup analyses, due to the limited sample size of patients for some subgroups within each study.

4.1.4.1 Relapse Rate

Analysis of relapse rate by subgroups was conducted and results of these analyses are presented in Figure 19. Overall, the efficacy of alemtuzumab 12 mg/day with respect to relapse rate appears to be uninfluenced by age, race, weight, and any of the clinical or MRI-related baseline disease characteristics analyzed (EDSS score, numbers of relapses within the last 1 or 2 years, T2 hyperintense lesion volume, BPF, presence of Gd-enhancing T1 lesions, and disease duration). The favorable treatment effect of alemtuzumab 12 mg/day over Rebif was observed consistently. Effects of gender and geographic region were observed on relapse rate, but in all groups alemtuzumab 12 mg/day had a favorable treatment effect compared with Rebif, and these effects were not duplicated in the other efficacy endpoints analyzed.

Figure 19: Subgroup Analyses for Relapse Rate



*Age, baseline EDSS, baseline brain volume, T2 lesion volume and disease duration are split at the sample median. Weight is split by quartiles.

Note: IPV denotes the p-value from the interaction test of treatment effect homogeneity.
MRI analyses include data from Phase 3 studies only (CAMMS324 and CAMMS323) due to differences in the MRI acquisition algorithms between the Phase 2 and Phase 3 studies.

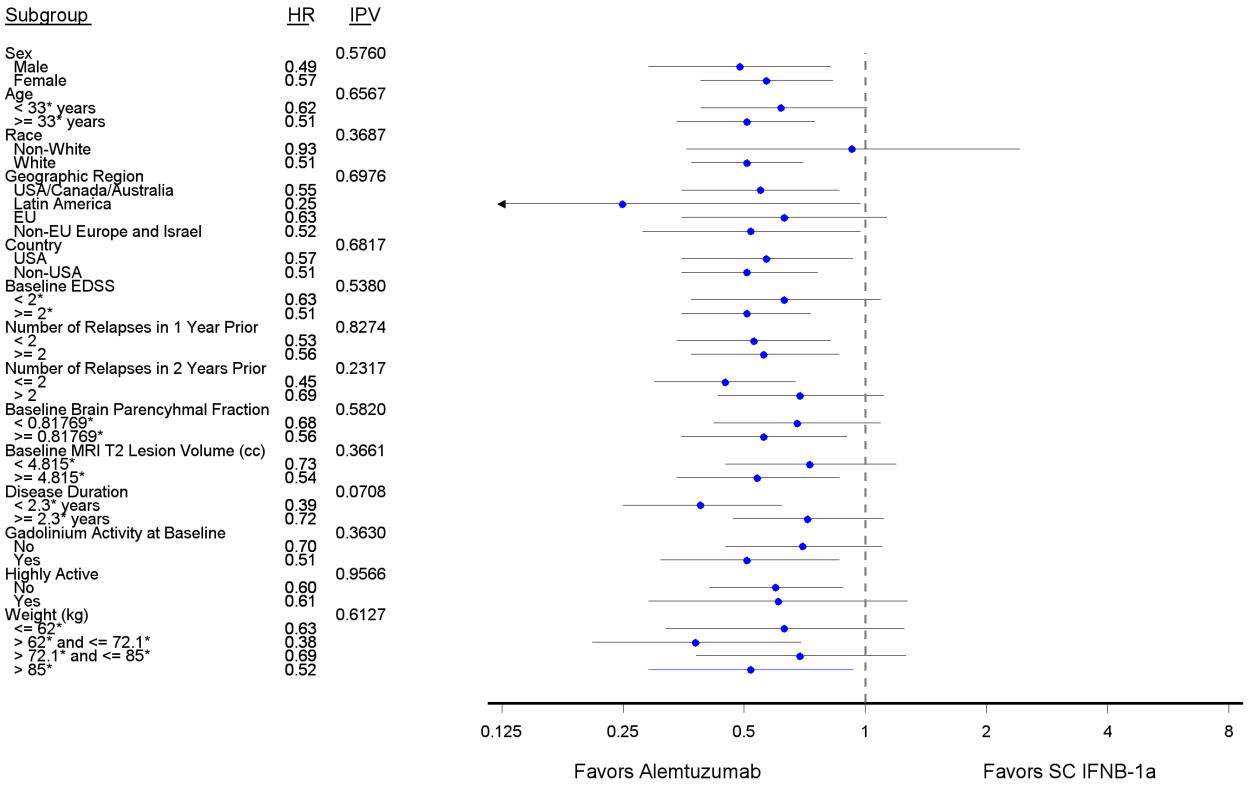
Geographic regions: EU includes Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, and United Kingdom. Latin America includes Argentina, Brazil, and Mexico. Non-EU Europe and Israel includes Croatia, Israel, Russia, Serbia, and Ukraine

Highly Active = 2 or more relapses in the prior year and a gadolinium-enhancing lesion at Baseline; Gadolinium Activity at Baseline = at least 1 Gd-enhanced T1 lesion at baseline.

4.1.4.2 Time to 6-Month Sustained Accumulation of Disability

Analysis of subgroups was conducted for time to 6-month SAD (Figure 20). There was a consistent, favorable treatment effect of alemtuzumab 12 mg/day on SAD compared with Rebif, regardless of gender, age, race, weight, geographic region, or baseline disease characteristics or imaging parameters, and all interaction tests between subgroup and treatment were non-significant.

Figure 20: Subgroup Analyses for 6-Month Sustained Accumulation of Disability



*Age, baseline EDSS, baseline brain volume, T2 lesion volume and disease duration are split at the sample median. Weight is split by quartile.

Note: IPV denotes the p-value from the interaction test of treatment effect homogeneity.
MRI analyses include data from Phase 3 studies only (CAMMS324 and CAMMS323) due to differences in the MRI acquisition algorithms between the Phase 2 and Phase 3 studies.

Geographic regions: EU includes Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, and United Kingdom. Latin America includes Argentina, Brazil, and Mexico. Non-EU Europe and Israel includes Croatia, Israel, Russia, Serbia, and Ukraine

Highly Active = 2 or more relapses in the prior year and a gadolinium-enhancing lesion at Baseline; Gadolinium Activity at Baseline = at least 1 Gd-enhanced T1 lesion at baseline

4.2 Extension Study CAMMS03409

The possibility that alemtuzumab's effects on MS relapse, brain lesion formation and disability status may be durable was suggested by significant treatment effects scored at 3 years in the Phase 2 study CAMMS223 and in the subgroup followed through 5 years (Coles, 2012, *Neurology*), and also by pilot studies (Coles, 2006, *J Neurol*). Interim data from the ongoing alemtuzumab MS Extension Study are similarly suggestive. Extension data through 31 December 2011 for patients from the Phase 3 studies CAMMS324 and CAMMS323 are summarized in Section 4.2. These summaries included 289 patients who had received IFNB-1a in a prior study and 735 patients who had received alemtuzumab 12 mg/day in a prior study.

While relapses were not RAP adjudicated in the Extension study, the relapse rates observed for patients who had received alemtuzumab 12 mg/day in a prior study (Table 22) were similar to the alemtuzumab group rates observed in the prior studies and lower than rates for the IFNB-1a groups in the prior studies, suggesting a durable treatment effect. The relapse rates for patients treated with IFNB-1a in the prior studies who then crossed over to receive alemtuzumab 12 mg/day in the Extension Study, were lower in the Extension Study than in the prior studies, suggesting that these patients benefited from alemtuzumab treatment.

Table 22: Relapse Results in the Extension Study CAMMS03409

Study Prior to Extension	Time Period	Statistic	IFNB-1a Crossover to Alemtuzumab	Alemtuzumab 12 mg/day
CAMMS324			**N=145**	**N=386**
	Year 1	Patients with any event, n	8	56
		Total number of events, n	9	61
		Annualized rate (95% CI)	0.09 (0.04, 0.20)	0.24 (0.16, 0.35)
	Year 2	Patients with any event, n	9	58
		Total number of events, n	10	67
		Annualized rate (95% CI)	0.11 (0.05, 0.21)	0.26 (0.19, 0.36)
CAMMS323			**N=144**	**N=349**
	Year 1	Patients with any event, n	15	64
		Total number of events, n	17	75
		Annualized rate (95% CI)	0.11 (0.06, 0.22)	0.20 (0.12, 0.34)
	Year 2	Patients with any event, n	19	72
		Total number of events, n	23	88
		Annualized rate (95% CI)	0.13 (0.07, 0.24)	0.19 (0.12, 0.32)

Note: There is insufficient follow-up to summarize relapse rates beyond Year 2.

Patients treated with alemtuzumab in the prior studies continued to have low rates of SAD during extended follow up through 3 years, after which there were too few patients for reliable inference (data not shown). Similarly, for patients treated with alemtuzumab 12 mg/day for the first time in the Extension Study (the Rebif extension study crossovers), the SAD rates appear to be consistent with the alemtuzumab 12 mg/day groups in the prior studies through 12 months of Extension Study follow up, after which there were too few patients for reliable inference (data not shown).

Of patients who received alemtuzumab 12 mg/day in the prior Phase 3 study, most (~80%) did not receive retreatment during Extension years 1 or 2. For those patients, alemtuzumab was last

administered at Month 12 of the prior study, and results obtained after Extension Years 1 and 2 represent outcomes 24 or 36 months post-treatment, respectively. The preliminary finding that relapse and disability progression rates remained low during these latter years (data not shown) supports the conclusion that alemtuzumab may have an exceptionally durable treatment effect.

4.3 Efficacy Conclusions

Alemtuzumab significantly reduced the occurrence of relapses compared to Rebif in each of the 3 active-controlled clinical trials. This significant treatment effect over an established MS therapy also translated into clinically meaningful benefits such as reductions in the rates of severe relapses, relapses treated with steroids, and relapses that led to hospitalization, as well as increases in the percentage of patients who did not experience any relapses during follow up. Further, a comprehensive set of sensitivity analyses demonstrated that the influence of factors such as unblinded EDSS raters or patient dropout had a negligible impact on the primary relapse analysis in the Phase 3 studies. Subgroup analyses were consistent over demographic and clinical characteristics, contributing to the overall robustness of the relapse findings.

The prevention of the accrual of permanent neurological impairment is another primary goal of MS therapy. In the Phase 3 study of treatment-naïve patients (CAMMS323), disability scores in both treatment groups were remarkably stable over the 2 years of observation. The rate of SAD was lower among alemtuzumab-treated patients than among Rebif-treated patients, but the difference was not statistically significant. Although Study CAMMS323 was large enough and of the appropriate duration based on historical assumptions, the very low SAD rate in the Rebif group may have limited the ability to detect an alemtuzumab treatment effect on the disability co-primary endpoint. The 2-year rate of SAD among Rebif-treated patients was lower than in previous controlled clinical studies of SC Rebif in MS (Ebers, 1998, *The Lancet*; European Medicines Agency, 2006, *Rebif EPAR*).

In contrast to results from Phase 3 study CAMMS323, treatment-naïve patients who received alemtuzumab 12 mg/day in the Phase 2 Study CAMMS223 experienced a significantly reduced risk of SAD compared with patient receiving Rebif. The rate of SAD in the Rebif group was higher than in CAMMS323 and close to the expected historical rate. Although patients in both CAMMS223 and CAMMS323 were treatment-naïve, the differences in baseline MRI characteristics in the 2 studies and the relative timing of patient recruitment suggest that treatment-naïve patients in the Phase 3 study may have had milder disease (less active and/or lower disease burden) than patients in the Phase 2 study at study entry. Their short duration of disease (median 1.5 years from onset in CAMMS323) is consistent with a stage at which

neurological deficits can still be compensated by unaffected brain areas and therefore below the threshold of clinical detection (see Figure 1).

In a study population of patients who relapsed while on prior MS therapy (CAMMS324; a population of patients including those with more severe disease), alemtuzumab significantly reduced the risk of SAD compared with Rebif. Patients treated with alemtuzumab also showed an improvement from baseline in mean EDSS score (while the EDSS scores of Rebif-treated patients worsened) and were significantly more likely to experience sustained reduction in EDSS scores than patients treated with Rebif, indicating an improvement in pre-existing disability. Unlike EDSS mean change, SRD has a straightforward interpretation that is clinically meaningful: the percentage of patients with substantial and durable improvement in disability score. Other measures of disability such as the MSFC and Sloan charts corroborated the impact of alemtuzumab on EDSS-based endpoints. As with the relapse rate, sensitivity and subgroup analyses underscored the consistency and robustness of the disability results in CAMMS324. Patients treated with alemtuzumab in CAMMS223 also had an improvement from baseline in mean EDSS score (while the EDSS scores of Rebif-treated patients worsened) and were more likely to experience SRD than patients receiving Rebif.

The MRI findings provide additional objective evidence that alemtuzumab is more effective than Rebif for treating patients with RRMS. High-dose Rebif was previously shown to have a beneficial impact on diverse MRI outcomes (Ebers, 1998, *The Lancet*; Li, 1999, *Ann Neurol*; Francis, 2005, *Neurology*) superior to that of intramuscular IFNB-1a (Avonex) (Panitch, 2002, *Neurology*), so testing alemtuzumab against this active comparator set a high hurdle for detecting a treatment effect on MRI measures. Alemtuzumab significantly reduced the risk of Gd-enhancing, T2-hyperintense, and T1-hypointense lesions compared to Rebif and significantly reduced the rate of brain atrophy (as measured by BPF) compared with Rebif.

Patients treated with alemtuzumab in the Phase 2 and Phase 3 studies who enrolled in Extension Study CAMMS03409 have stably reduced ARR and continued to have low rates of SAD during the first two years of the Extension Study. These findings are consistent with the 3-year data from CAMMS223 indicating that alemtuzumab's efficacy benefit is durable. While the majority of patients enrolled in the Phase 3 studies went on to enroll in the CAMMS03409 Extension Study, only about 20% (199 patients of 1015) who had received alemtuzumab in a prior study received re-treatment with alemtuzumab. Patients who received IFNB-1a in either of the prior Phase 3 studies and who crossed over to receive alemtuzumab in the Extension Study showed a lower ARR and reduced risk of SAD after alemtuzumab treatment than during their prior

treatment with Rebif, suggesting that these patients benefited from alemtuzumab treatment. SAD rates for these patients over the first 12 months of alemtuzumab treatment were consistent with rates observed for patients in the 12-mg groups in the Phase 3 studies.

The clinical findings and the MRI results and the concordance of effects across a diverse range of endpoints and subgroups demonstrate that alemtuzumab is effective in a broad range of relapsing MS patients, supporting the proposed indication in MS.

5. Overview of Safety

5.1 Safety Database for Alemtuzumab, Including Campath Experience

The safety profile for MS is based on a large safety database derived from one Phase 2 study, two Phase 3 studies, plus the ongoing Extension Study CAMMS03409. This data set comprises complete safety data on nearly 1,500 MS patients exposed to alemtuzumab with more than 5400 patient-years of exposure. The profile seen across the program demonstrates that the safety findings are predictable, thus, susceptible to early identification.

Safety monitoring was designed in consideration of several factors. First was the pharmacology of the molecule. As a lymphocyte depleting antibody, there was the potential for cytokine release to manifest as infusion associated reactions and infections as result of the degree of depletion observed. Such events were in fact observed in clinical experience with Campath in oncology where severe infusion associated reactions and infections are part of the known profile in the B-CLL population using high dose regimen. Finally, the early experience in MS when giving the lower dose immunomodulatory regimen (12 mg) revealed events of autoimmune disorders, specifically thyroid disease, ITP and glomerulonephritis, each of which were specifically monitored for throughout the later part of the MS clinical development program.

Table 23 summarizes the protocol required risk minimization measures utilized in the Genzyme sponsored MS clinical studies.

Table 23: Protocol Risk Minimization Measures - Genzyme-Sponsored Clinical Studies of Multiple Sclerosis

Risk	Risk Minimization Measure(s)
Infusion-Associated Reactions	Methylprednisolone pretreatment (1,000 mg IV) on first 3 days of any treatment cycle Antihistamines and/or antipyretics as pretreatment or as needed for IAR management treatment at the investigator's discretion
Thyroid Disorders	Patient and investigator education on signs and symptoms of thyroid disorders Quarterly thyroid function tests for all patients
ITP	Patient and investigator education on signs and symptoms of ITP Monthly CBC testing for all patients Monthly symptom monitoring survey (offset by 2 weeks from blood testing) for all patients
Nephropathies	Monthly serum creatinine for alemtuzumab-treated patients only Monthly urinalysis for alemtuzumab-treated patients only Monthly symptom monitoring survey
Serious Infections	Acyclovir prophylaxis beginning on first day of any treatment course continuing for 28 days following the last infusion

5.1.1 Safety Experience with Campath

In addition to the clinical experience in MS, there is considerable information from clinical trials in B-CLL where alemtuzumab (Campath) was administered at higher and more frequent doses (i.e., 30 mg, 3 times per week for up to 12 weeks; total dose >1,000 mg). This is in contrast to the intended dosing regimen for alemtuzumab in MS where 2 treatment courses (one 5-day course and one 3-day course) of 12 mg/day are administered 12 months apart (total dose 96 mg).

Data from >10 years of post-marketing experience in B-CLL and from use of Campath in in other diseases (e.g., transplant) in >41,000 patients have also been analyzed (Appendix C, Section 10.3). These safety data allow for a more comprehensive understanding of the risks associated with use of alemtuzumab.

Specifically, a review of both clinical and post-marketing data indicate that IARs were among the most common adverse events associated with Campath in the oncology setting. IARs were often severe in nature and included serious reactions at the doses used in B-CLL experience. However, it is of note that the IAR profile as characterized in the B-CLL population is different from that observed in clinical trials in MS. While IARs were common in MS patients, such reactions were predominantly mild to moderate in severity with few patients experiencing serious events (refer to Section 5.1.8.1 for a discussion of IARs in the MS clinical experience).

Hematologic adverse events were also common in the B-CLL population, including leukopenia, neutropenia, thrombocytopenia, and anemia. Lymphopenia is an expected pharmacologic effect of alemtuzumab as CD52 is extensively expressed on T and B cells. Neutropenia, thrombocytopenia, and anemia, however, are likely due primarily to underlying bone marrow disease, residual bone marrow toxicity from prior chemotherapy, and from effects of concurrent treatments. It is known that patients with B-CLL have a risk for the development of cytopenias such as ITP likely related to the immune dysregulation associated with their underlying disease, with the background incidence of ITP roughly 2% in patients with hematological malignancies (Cheson, B.D., 2001. *Cancer: Principles and Practice of Oncology*.; Diehl, 1998, *Semin Oncol*).

Severe infections were common in patients treated with Campath for B-CLL. The risk of infection in B-CLL patients is variable, however all patients with B-CLL are at increased risk of opportunistic infections due to risk factors inherent to the disease: hypogammaglobulinemia, T-cell dysfunction, neutropenia, phagocyte defects, complement dysfunction. Therefore, infection is a major cause of morbidity and mortality in B-CLL (Anaissie, 1998, *Ann Intern Med*; Morrison, 1998, *Semin Oncol*). Up to 80% of patients with B-CLL will experience an infection, ranging from moderate to life threatening, during the course of their disease (Anaissie, 1998, *Ann Intern Med*). The stage of disease (Rai [Rai, 1975, *Blood*] or Binet stage [Binet, 1981, *Cancer*]) and intensity of previous therapy is clearly correlated with the incidence of infection and median survival in these patients (Anaissie, 1998, *Ann Intern Med*; Morrison, 1998, *Semin Oncol*; Cheson, 1995, *J Clin Oncol*; Fenchel, 1995, *Leuk Lymphoma*; Chapel, 1987, *Semin Hematol*).

While the experience with alemtuzumab in B-CLL provides a useful background to assess potential events that could occur during use in MS, its applicability to an MS population is limited by the significant differences in dose regimen and patient population (comorbidities, underlying disease and the general geriatric age of B-CLL patients). Accordingly, the safety analysis that follows if focused on the clinical experience in clinical trials in MS and B-CLL data is not further discussed. A summary of the safety information gathered from clinical and post-marketing experience with Campath is provided in Appendix C, Section 10.3 of this document.

5.1.2 Pooling of Safety Data

Safety data from the Phase 2 study CAMMS223 and Phase 3 studies CAMMS323 and CAMMS324 were analyzed individually at the conclusion of each study. Because all 3 studies were conducted in patients with RRMS using the same treatment regimen (i.e., annual courses of 12 mg/day and/or 24 mg/day alemtuzumab) and comparator, and given that the results were

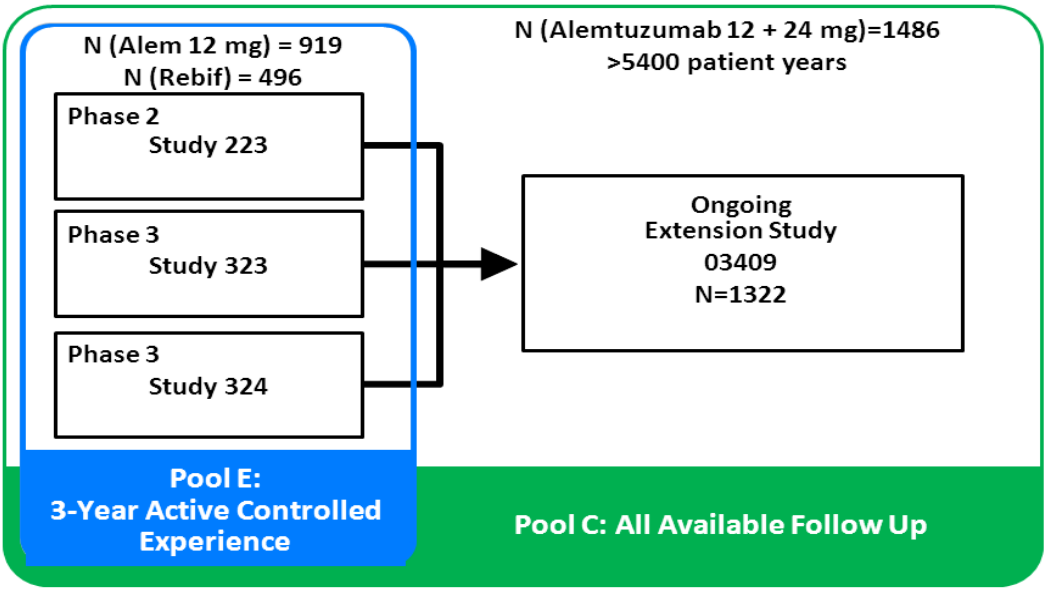
generally consistent across studies in terms of the risks identified, individual results from the active controlled experience were pooled to facilitate more in-depth integrated safety analysis.

Six analysis pools were defined for the purposes of integrated safety analysis and were comprised of different study populations and varying periods of follow-up (e.g., Phase 2 and 3 patients with 2 or 3 years of follow up, Phase 3 patients only, treatment naïve patients only, all patients over all follow-up). This report focuses primarily on safety data in the 2 most comprehensive analysis pools (Figure 21):

1) Pool E: All active-controlled studies - 3-year follow up - (CAMMS223, CAMMS323, CAMMS324): All safety data through 3 years after first study treatment with comparison to Rebif (i.e., all data from the 2-year Phase 3 studies plus 3-year data from the Phase 2 study). This represents the entire active-controlled safety database for alemtuzumab and is referred to henceforth as "active-controlled experience".

2) Pool C: All alemtuzumab-treated patients over all available follow up - (patients from CAMMS223, CAMMS323, CAMMS324, and CAMMS03409): All available safety data in all MS patients exposed to at least 1 dose of alemtuzumab in clinical trials through 26 November 2012. This pool provides an inclusive overview of safety of alemtuzumab with regard to long-term follow up (up to 10 years for some patients) and is referred to henceforth as the "all available follow-up" population. This population is the focus of analysis when discussing serious events or events of interest where cumulative exposure and extended follow-up are most relevant.

Figure 21: Safety Analysis Pools in Briefing Document



5.1.3 Patient Exposure and Duration of Follow-up

5.1.3.1 Active-controlled Experience

A total of 1,684 patients with RRMS received study treatment (Rebif or alemtuzumab) in the active-controlled studies; 496 patients received Rebif 3 times weekly, and 1,188 patients received alemtuzumab (919 patients received annual cycles of alemtuzumab 12 mg/day and 269 patients received annual cycles of 24 mg/day). Patients who initially received 24 mg/day alemtuzumab and later received 12 mg/day doses are counted in the 24 mg/day treatment group. The duration of follow-up in the active-controlled experience is shown in Table 24.

Table 24: Duration of Follow-up in 3-Year Active-Controlled Experience (Pool E)

	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 mg + 24 mg (N=1188)
Months of follow-up			
Mean (SD)	24.4 (6.97)	25.3 (3.98)	26.1 (4.77)
Median	24.0	24.1	24.2
Min, Max	0.1, 39.1	8.9, 38.5	8.9, 38.5
Total person-years	1007.57	1938.21	2580.46

5.1.3.2 All Available Follow-up

As of 26 November 2012, a total of 1,486 patients have received alemtuzumab including 298 patients who had received Rebif in a prior study and then received alemtuzumab in the Extension Study (CAMMS03409).

A total of 1,217 (82%) patients were in the 12 mg/day alemtuzumab group and 269 (18%) were in the 24 mg/day alemtuzumab group. A total of 1,322 patients were ever enrolled in the Extension Study.

The duration of follow-up and exposure through 26 November 2012 are provided in Table 25.

Table 25: Duration of Follow-up and Exposure to Alemtuzumab through All Available Follow-up (Pool C)

	Alemtuzumab 12 mg/day (N=1217)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab 12 mg + 24 mg (N=1486)
Months of follow-up			
Mean (SD)	40.6 (17.66)	57.1 (23.73)	43.6 (19.93)
Median	41.8	47.4	43.2
Min, Max	8.9, 112.3	10.0, 117.3	8.9, 117.3
Total person years	4121.55	1279.12	5400.67
Total number of cycles received			
1 cycle	53 (4.4)	9 (3.3)	62 (4.2)
2 cycles	914 (75.1)	164 (61.0)	1078 (72.5)
3 cycles	200 (16.4)	72 (26.8)	272 (18.3)
4 cycles	46 (3.8)	19 (7.1)	65 (4.4)
5 cycles	4 (0.3)	5 (1.9)	9 (0.6)

Note: All percentages are based on the number of alemtuzumab-treated patients in the corresponding treatment group, except that the percentages in the rows under each cycle are based on the number of alemtuzumab-treated patients who received that specific cycle in the corresponding treatment group.

Overall, the median duration of follow-up for all alemtuzumab-treated patients (n=1,486) was 43.2 months for a total of 5400.67 person-years of follow-up. A total of 1241 (83.5%) alemtuzumab-treated patients had at least 2 years of follow-up; 1078 (72.5%) had at least 3 years of follow-up; and 444 (29.9%) had at least 4 years of follow-up.

5.1.4 Adverse Events

A summary of adverse events in the alemtuzumab clinical studies is provided in Table 26.

Table 26: Overview of Adverse Events in the 3-Year Active Controlled Experience (Pool E)

AEs, n (%)	IFNB-1a (N=496)	Alemtuzumab 12 mg (N=919)	Alemtuzumab 12 mg + 24 mg (N=1188)
All events	470 (94.8)	897 (97.6)	1163 (97.9)
Grade 1	401 (80.8)	817 (88.9)	1068 (89.9)
Grade 2	405 (81.7)	840 (91.4)	1099 (92.5)
Grade 3	110 (22.2)	232 (25.2)	328 (27.6)
Grade 4	10 (2.0)	27 (2.9)	42 (3.5)
Serious AEs	96 (19.4)	177 (19.3)	228 (19.2)
Deaths	1[a]	4 (0.4)	5 (0.4)
AEs leading to treatment discontinuation	39 (7.9)	22 (2.4)	29 (2.4)
AEs leading to study discontinuation	21 (4.2)	3 (0.3)	4 (0.3)

[a]This death in a patient treated with IFNB-1a occurred during the extension period of Phase 2 Study CAMMS223

Over 3 years of experience in all active controlled studies, most patients in both treatment groups reported at least 1 AE, the majority of which were mild (Grade 1) or moderate (Grade 2) in severity. Severe (Grade 3) or life-threatening (Grade 4) AEs were reported for a similar proportion of patients in the alemtuzumab 12 mg/day and Rebif groups.

5.1.4.1 Common AEs

Active-controlled Experience

Over 3 years of experience in all active-controlled studies, the incidence of adverse events was similar between groups. The 3 most frequently affected MedDRA SOCs in the alemtuzumab 12 mg/day treatment group were 'Skin and subcutaneous tissue disorders' (77.9%), 'Nervous system disorders' (73.4%), and 'Infections and infestations' (71.6%).

Adverse events reported for >10% of patients in any treatment group are summarized in Appendix D, Section 10.4. Adverse events reported for >10% of patients in the alemtuzumab 12 mg/day group and at a greater frequency than that observed in the Rebif group included (in descending frequency): headache, rash, pyrexia, nasopharyngitis, nausea, fatigue, UTI, insomnia, urticaria, pruritus, upper respiratory tract infection, pain in extremity, paraesthesia, arthralgia, back pain, diarrhoea, sinusitis, oropharyngeal pain, and vomiting.

Adverse events reported for >10% of patients in the Rebif group and at a greater frequency than the alemtuzumab 12 mg/day group included (in descending frequency): MS relapse, influenza like illness, injection site erythema, depression and muscular weakness.

The majority of AEs that occurred in the alemtuzumab group were events associated with infusions (IARs) and are described in detail in Section 5.1.8.1.

5.1.5 Serious Adverse Events

Over 3 years of follow up in all active-controlled studies, the incidence of SAEs was consistent between treatment groups; 19.3% of patients treated with alemtuzumab 12 mg/day and 19.4% of patients treated with Rebif (Table 27). The most common serious adverse event in both groups was MS relapse, though this occurred more frequently in patients receiving Rebif.

Table 27: Serious Adverse Events in 2 or More Patients in Alemtuzumab 12 mg/day Group, Year Active Controlled Experience

SAEs, n (%)	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg/day (N=1188)
Any SAE	96 (19.4)	177 (19.3)	228 (19.2)
Multiple sclerosis relapse	51 (10.3)	57 (6.2)	64 (5.4)
Autoimmune thrombocytopenia	0 (0.0)	5 (0.5)	8 (0.7)
Appendicitis	2 (0.4)	4 (0.4)	4 (0.3)
Gastroenteritis	0 (0.0)	4 (0.4)	6 (0.5)
Pneumonia	0 (0.0)	4 (0.4)	5 (0.4)
Urticaria	0 (0.0)	4 (0.4)	5 (0.4)
Pyrexia	0 (0.0)	3 (0.3)	4 (0.3)
Syncope	0 (0.0)	3 (0.3)	3 (0.3)
Thyroid cancer	0 (0.0)	3 (0.3)	3 (0.3)
Abdominal pain	1 (0.2)	2 (0.2)	2 (0.2)
Agranulocytosis	0 (0.0)	2 (0.2)	2 (0.2)
Angioedema	0 (0.0)	2 (0.2)	2 (0.2)
Atrial fibrillation	0 (0.0)	2 (0.2)	2 (0.2)
Basedow's disease	0 (0.0)	2 (0.2)	3 (0.3)
Chest discomfort	0 (0.0)	2 (0.2)	2 (0.2)

Table 27: Serious Adverse Events in 2 or More Patients in Alemtuzumab 12 mg/day Group, Year Active Controlled Experience

SAEs, n (%)	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg/day (N=1188)
Chest pain	0 (0.0)	2 (0.2)	2 (0.2)
Cholecystitis	3 (0.6)	2 (0.2)	2 (0.2)
Cholecystitis acute	0 (0.0)	2 (0.2)	2 (0.2)
Foot fracture	0 (0.0)	2 (0.2)	2 (0.2)
Headache	1 (0.2)	2 (0.2)	4 (0.3)
Herpes zoster	0 (0.0)	2 (0.2)	4 (0.3)
Hyperthyroidism	0 (0.0)	2 (0.2)	2 (0.2)
Hypotension	0 (0.0)	2 (0.2)	2 (0.2)
Hypothyroidism	0 (0.0)	2 (0.2)	3 (0.3)
Idiopathic thrombocytopenic purpura	0 (0.0)	2 (0.2)	4 (0.3)
Incorrect dose administered	0 (0.0)	2 (0.2)	2 (0.2)
Infusion related reaction	0 (0.0)	2 (0.2)	2 (0.2)
Menometrorrhagia	0 (0.0)	2 (0.2)	3 (0.3)
Migraine	0 (0.0)	2 (0.2)	3 (0.3)
Nausea	1 (0.2)	2 (0.2)	3 (0.3)
Nephrolithiasis	0 (0.0)	2 (0.2)	2 (0.2)
Ovarian cyst	0 (0.0)	2 (0.2)	2 (0.2)
Pneumonia aspiration	0 (0.0)	2 (0.2)	2 (0.2)
Road traffic accident	0 (0.0)	2 (0.2)	2 (0.2)
Sinus tachycardia	0 (0.0)	2 (0.2)	3 (0.3)
Tachycardia	0 (0.0)	2 (0.2)	2 (0.2)
Tooth infection	0 (0.0)	2 (0.2)	2 (0.2)
Uterine leiomyoma	1 (0.2)	2 (0.2)	2 (0.2)

In the active-controlled studies, the most frequently reported SAEs (occurred in ≥0.4% of patients) in the alemtuzumab 12 mg/day group were MS relapse (6.2%), autoimmune thrombocytopenia (0.5%), appendicitis (0.4%), gastroenteritis (0.4%), pneumonia (0.4%), , and urticaria (0.4%). Events more common on alemtuzumab generally fell into the categories of

those events associated with infusions, infections, and autoimmune disease, areas previously identified as potential risks of alemtuzumab treatment.

5.1.6 Adverse Events Leading to Treatment or Study Discontinuation

Treatment discontinuation was defined as permanent discontinuation of treatment (i.e., alemtuzumab or Rebif). Patients who discontinued treatment could remain in the study and continue to be followed for efficacy and safety. Patients who developed ITP or anti-glomerular basement membrane (anti-GBM) disease were discontinued from any further treatment per study protocol.

Study discontinuation was defined as permanent discontinuation from study participation.

In the active-controlled studies over 3 years of follow up the proportion of patients who discontinued treatment due to an AE was higher in the Rebif group (7.9%) than in the alemtuzumab 12 mg/day group (2.4%). The AEs leading to treatment discontinuation in more than 1 patient in the alemtuzumab 12 mg/day group were non-cardiac chest pain (3 patients) and hypothyroidism, infusion related reaction, MS relapse, dyspnoea (2 patients each). The most common AEs leading to treatment discontinuation of Rebif were MS relapse (5 patients), influenza-like illness (4 patients), hepatic enzyme increased (3 patients), and lymphopenia, thrombocytopenia, injection site erythema, injection site pain, pyrexia, depression, mood altered (2 patients each).

Three (0.3%) patients discontinued the study in the alemtuzumab 12 mg/day group and 21 (4.2%) patients discontinued the study in the Rebif group. The AEs leading to study discontinuation in the alemtuzumab 12 mg/day group were infusion-associated reaction (1 patient), non-cardiac chest pain (1 patient), and MS relapse (1 patient). One patient in the alemtuzumab 12 mg/day group and 6 patients in the Rebif group had an SAE leading to study discontinuation.

5.1.7 Deaths

A total of 9 deaths that occurred over 9 years of follow up; 8 deaths occurred in patients who received alemtuzumab (out of 5401 total person-years) and 1 in a patient who received Rebif (out of 1008 total person-years). Most deaths were associated with accidents or other unrelated causes in patients. However, there were two deaths secondary to complications of alemtuzumab treatment.

The most recent was a case of sepsis that developed in a patient with autoimmune pancytopenia in the Extension study. This patient was identified with pancytopenia through routine monitoring and responded to first line treatment with corticosteroids. The patient prematurely discontinued steroid treatment upon return to his home in a remote location that was many hours from medical care and he experienced a recurrence of pancytopenia and subsequent infection. The second was the index case of ITP that occurred in the Phase 2 study CAMMS223 prior to the implementation of the ITP monitoring program. This patient had symptoms of immune thrombocytopenia that went unrecognized until he experienced a fatal hemorrhage. Since the implementation of the ITP monitoring program, all subsequent events of ITP have been identified early and successfully treated resulting in recovery (see Section 5.1.8.3).

A complete listing of deaths that occurred during Genzyme-sponsored alemtuzumab clinical studies is provided in Table 28.

Table 28: Listing of All Deaths in Alemtuzumab Clinical Studies

Study	Age/Sex	Treatment Group	Time (months since last dose)	Cause of Death	Relevant History
CAMMS223	32/male	IFNB-1a		Hit by train	Alcohol abuse, depression
	39/male	24 mg/day	7	ITP and cerebral hemorrhage	Index case of ITP
	45/female	12 mg/day	2	Cardiovascular disorder	Multiple risk factors, e.g., obesity, hypertension, smoking
CAMMS323	32/male	12 mg/day	9	Motorcycle accident	None
CAMMS324	30/female	12 mg/day	8	Hit by car	None
	32/male	12 mg/day	10	Aspiration pneumonia	Severe, disabling MS relapse 1 year prior
CAMMS03409	28/male	12 mg/day	3	Incised wound	Poor mobility, fall
	52/male	12 mg/day	13	Unknown	Patient found dead at home, presumed accidental
	46/male	12 mg/day	20	Sepsis	Associated with pancytopenia

5.1.8 Safety Events of Interest

As noted above in the analyses of common and serious adverse events, events more common on alemtuzumab were most often those events associated with infusion reactions, infections, and autoimmune disease, areas previously identified as potential risks of alemtuzumab treatment from both the B-CLL experience with Campath and the pilot studies performed in MS patients. The remaining analysis will focus on key events that fall into these categories of interest. The discussion will focus primarily on the 12 mg/day dose group as this is the dose being proposed for marketing. However, experience from the 24 mg/day dose will be noted when there are differences from that seen with the 12 mg/day dose. Further, while the active controlled experience versus Rebif will be discussed, cumulative alemtuzumab exposure and extended follow-up are increasingly important as many events of interest were not commonly observed or occurred remote to alemtuzumab dosing. Therefore, pooled analyses combining 12 mg/day and 24 mg/day dose groups were performed in addition to 12 mg/day alone and adverse events were assessed over the entire alemtuzumab experience.

5.1.8.1 Infusion-Associated Reactions

Infusion-associated reactions are frequently associated with monoclonal antibodies (Dillman, 1999, *Cancer Metastasis Rev*) and were described in association with alemtuzumab treatment both in association with the treatment of B-CLL as well as in the early pilot studies in MS (Coles, 1999, *Ann Neurol*). Pilot MS studies also suggested a need for high-dose corticosteroid premedication during the first 3 days of each treatment course to ameliorate/reduce such IARs and fluctuation of old MS symptoms (Coles, 1999 *Ann Neurol*; Coles, 2006, *J Neurol*). Patients in both treatment groups the MS clinical program received pre-treatment with IV steroids (1 g of methylprednisolone) on the first 3 days of any alemtuzumab treatment course. Antihistamine and/or antipyretic treatment could also be administered at the investigator's discretion. Patients in the Rebif group received corticosteroids annually throughout the active controlled portion of the studies.

IARs were defined as AEs that occur between the start of any alemtuzumab infusion and also within 24 hours following the completion of the infusion. For the purpose of comparison, IARs in Rebif patients were defined as any AEs occurring during annual course of methylprednisolone with follow-up to match alemtuzumab: 6 days for course 1 and 4 days for course 2.

IARs were very common in alemtuzumab treated patients; the overall incidence of IARs was 91.1% in the alemtuzumab 12 mg/day group in the active controlled experience Table 29.

Table 29: Incidence of Infusion Associated Reactions (IARs) in the Alemtuzumab Clinical Studies

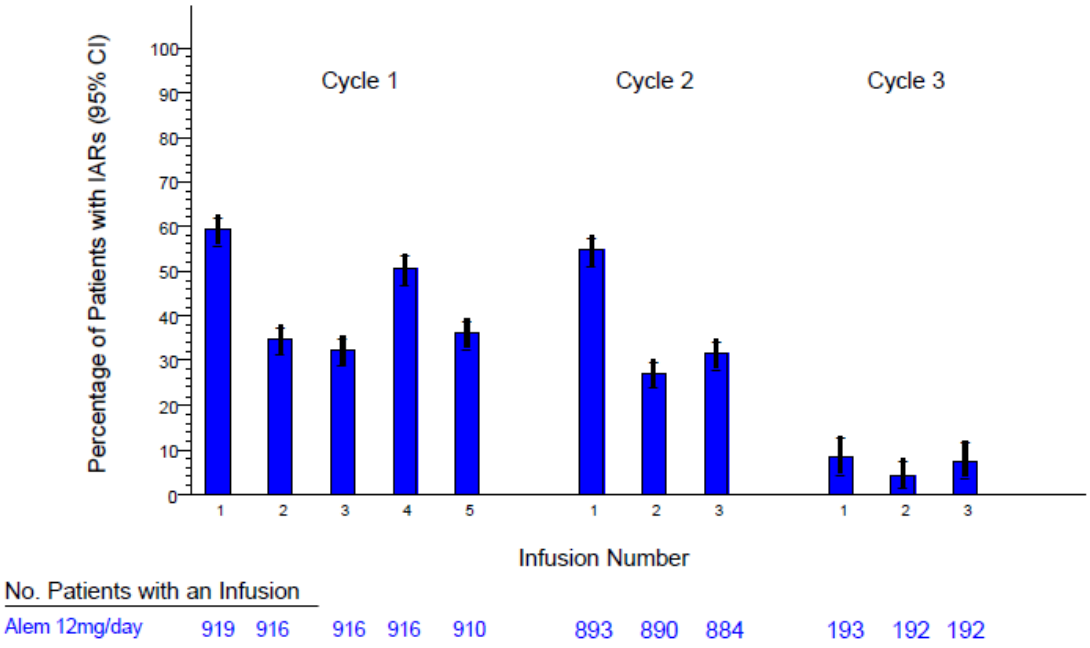
	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
IARs	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg/day (N=919)**	**Alemtuzumab 12 + 24 mg/day (N=1486)**
AEs, n (%)	217 (43.8)	837 (91.1)	1366 (91.9)
Grade 1	170 (34.3)	628 (68.3)	1015 (68.3
Grade 2	113 (22.8)	686 (74.6)	1160 (78.1)
Grade 3	1 (0.2)	80 (8.7)	139 (9.4)
Grade 4	0	5 (0.5)	9 (0.6)
SAEs	3 (0.6)	26 (2.8)	39 (2.6)
IARs leading to treatment discontinuation	1 (0.2)	7 (0.8)	17 (1.1)

The most common IARs (occurring in ≥ 10% of patients) were headache, rash, pyrexia, nausea, urticaria, pruritus, insomnia, flushing and chills. Few IARs led to treatment discontinuation (0.8% discontinued alemtuzumab treatment due to an IAR).

Grade 4 IARs occurred in 0.5% of patients in alemtuzumab 12 mg group and included non-cardiac chest pain, dyspnea, tachycardia, atrial fibrillation, chills, generalized rash and angioedema.

The tolerability of the alemtuzumab 12 mg/day dose was improved compared to that of the 24 mg/day dose. Incidences of IARs were generally higher in the alemtuzumab 24 mg/day group with a higher incidence also of severe (Grade 3 and 4) IARs. However, there were no notable differences between the alemtuzumab 12 mg/day and 24 mg/day groups with regards to the preferred terms of common IARs reported. The greatest number of IARs occurred on the first infusion day of each cycle and decreased thereafter with subsequent treatment courses.

Figure 22: Frequency of IARs by Infusion Day, 3-Year Active Controlled Experience (12 mg)



Analysis of Potential Anaphylactic Events

In order to fully assess for the possibility of anaphylactic reactions during alemtuzumab infusions, 3 separate searches of AE PTs were performed using the following search criteria moving from the most specific search to the most sensitive:

- PTs specific for anaphylaxis (derived from Category A of the MedDRA Anaphylaxis SMQ)
- A modified version of the MedDRA SMQ for anaphylaxis based on the Second National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network symposium definition of anaphylaxis (Sampson, 2006, J *Allergy Clin Immunol*)
- A 3-tiered search identifying events involving combinations of single event terms within multiple PT categories (e.g., rash and wheezing) to ensure that no events were missed using searches from one category alone given that anaphylactic reactions often manifest themselves in multiple classes of symptoms.

No cases of anaphylaxis were identified during the active-controlled experience. Over all available follow-up, these analyses revealed a single patient who experienced an event of anaphylaxis (reported as an anaphylactoid reaction):

- 23-year old female with medical history of ulcerative colitis, drug hypersensitivity (aspirin, ciprofloxacin, sulfonamides), seasonal allergy, rash and obesity received 2 cycles of alemtuzumab 24 mg/day in CAMMS324, and had experienced non-serious IARs of pruritus (Grade 1) and dyspnea (Grade 3) during Cycle 2; the event of dyspnea required temporary interruption of alemtuzumab. The patient developed Grade 4 serious anaphylactoid reaction on the first day of the 3rd cycle (12mg/day) in the Extension Study (CAMMS03409). Patient experienced redness and swelling of eyes, lips, hands and face; itching and swelling in mouth and throat with cough. Alemtuzumab treatment was discontinued. The patient was treated with epinephrine, diphenhydramine, and oxygen via nasal cannula, and recovered without sequelae.

5.1.8.2 Infections

Prospective studies have shown that patients with RRMS have 1.2 to 1.4 systemic infections per year (Buljevac, 2002, *Brain*; Correale, 2006, *Neurology*). These infections occurred predominantly in the upper respiratory, urinary, and gastrointestinal tracts.

Given that lymphocyte depletion occurs as a result of the pharmacodynamic effect of alemtuzumab and may be prolonged prior to lymphocyte repopulation risk of infection was specifically assessed throughout the alemtuzumab MS program. Table 30 presents an overview of infection AEs in the alemtuzumab clinical studies.

Table 30: Overview of Infections in 3-Year Active Controlled Experience (Pool E)

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Infection AEs	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg (N=919)**	**Alemtuzumab 12 mg + 24 mg (N=1486)**
AEs, n (%)	269 (54.2)	660 (71.8)	1149 (77.3)
Grade 1	145 (29.2)	419 (45.6)	747 (50.3)
Grade 2	201 (40.5)	532 (57.9)	983 (66.2)
Grade 3	7 (1.4)	37 (4.0)	83 (5.6)
Grade 4	0	1 (0.1)	2 (0.1)
SAEs	6 (1.2)	27 (2.9)	82 (5.5)

Table 30: Overview of Infections in 3-Year Active Controlled Experience (Pool E)

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Infection AEs	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg (N=919)**	**Alemtuzumab 12 mg + 24 mg (N=1486)**
Infections leading to treatment discontinuation	0	0	2 (0.1)
Overall rate of infections	0.647	1.228	1.040

Infections were common in both treatment groups but more frequently reported in alemtuzumab-treated patients compared with Rebif-treated patients. In the active-controlled experience, the incidence of infection AEs for the alemtuzumab 12 mg/day group was 71.8%, compared with 54.2% in the Rebif group. The majority of infections were mild or moderate in severity though more Grade 3 and 4 infections occurred in alemtuzumab treated patients (Table 30). There was a single fatal (Grade 5) case of sepsis, described in Section 5.1.7. Two patients discontinued treatment secondary to infection. The most frequently reported infections (≥ 5% of patients) for both the alemtuzumab 12 mg/day and Rebif groups were nasopharyngitis, UTI, upper RTI, sinusitis, and influenza, infections common in this population. Additionally, for the alemtuzumab 12 mg/day group, oral herpes (8.8%) bronchitis (7.1%) and rhinitis (4.6%) were frequent events (Table 31). Infections were generally of typical duration and resolved following conventional medical treatment.

The rate of infection over the 3-year was active-controlled experience was 1.228 per person-year in the alemtuzumab 12 mg/day group as compared with 0.647 per person year in the Rebif group.

Table 31: Infections Reported in ≥ 5% of Patients in the Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg/day (N=1486)
Preferred Term	**n (%)**	**n (%)**	**n (%)**
Any Event	**269 (54.2)**	**660 (71.8)**	**1149 (77.3)**
Nasopharyngitis	84 (16.9)	216 (23.5)	447 (30.1)
Urinary tract infection	42 (8.5)	164 (17.8)	366 (24.6)
Upper respiratory tract infection	58 (11.7)	145 (15.8)	307 (20.7)
Sinusitis	36 (7.3)	101 (11.0)	215 (14.5)
Oral herpes	7 (1.4)	81 (8.8)	134 (9.0)
Influenza	27 (5.4)	78 (8.5)	161 (10.8)
Bronchitis	16 (3.2)	65 (7.1)	156 (10.5)
Rhinitis	11 (2.2)	42 (4.6)	69 (4.6)
Herpes zoster	4 (0.8)	39 (4.2)	121 (8.1)
Pharyngitis	7 (1.4)	36 (3.9)	75 (5.0)
Gastroenteritis viral	12 (2.4)	30 (3.3)	88 (5.9)
Gastroenteritis	5 (1.0)	37 (4.0)	78 (5.2)

Serious Infections

In the active controlled experience, serious infections were reported in 2.9% of patients in the alemtuzumab 12 mg group as compared with 1.2% of those receiving Rebif (Table 32). Serious infections reported in ≥2 patients in the alemtuzumab 12 mg/day group were appendicitis, gastroenteritis, and pneumonia (each reported in 4 patients, 0.4%) and herpes zoster and tooth infection (each reported in 2 patients, 0.2%); appendicitis was the only serious infection reported in more than 1 patient in the Rebif group.

As noted above, one alemtuzumab-treated patient died due to sepsis following development of autoimmune pancytopenia after discontinuing prescribed steroid medication. No other infection-related deaths were reported in the clinical program over all follow-up.

Table 32: Incidence of Serious Infections in the Alemtuzumab Clinical Studies Occurring in ≥ 2 Patients

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Infection SAEs	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg/day (N=919)**	**Alemtuzumab 12 mg + 24/day mg (N=1486)**
Serious Infections, n (%)	6 (1.2)	27 (2.9)	82 (5.5)
Pneumonia	0	4 (0.4)	11 (0.7)
Herpes zoster	0	2 (0.2)	10 (0.7)
Gastroenteritis	0	4 (0.4)	7 (0.5)
UTI	0	1 (0.1)	7 (0.5)
Appendicitis	2 (0.4)	4 (0.4)	5 (0.3)
Cellulitis	0	0	4 (0.3)
Bronchitis	0	0	3 (0.2)
Sepsis	0	1 (0.1)	3 (0.2)
Subcutaneous abscess	0	0	3 (0.2)
Lower respiratory tract infection	0	0	2 (0.1)
Pyelonephritis	0	1 (0.1)	2 (0.1)
Tooth infection	0	2 (0.2)	2 (0.1)
Viral infection	0	0	2 (0.1)
Rate of serious infections	0.006	0.017	0.018

Infections over Time

The risk of infection over time was assessed over all available follow-up. Infections tended to occur early in the course of alemtuzumab treatment. The highest incidence of infections was observed in the first month after each treatment cycle (i.e., Month 1 and Month 13), and with the largest increase during the first month after initiation of the first treatment cycle. In addition, there was no increase in the risk of infection over time that would be indicative of cumulative immunosuppressive effects.

Over all available follow-up, the cumulative incidence for infections in alemtuzumab-treated patients decreased each year from Years 1 to 4 in the alemtuzumab 12 mg/day treatment group (56.9%, 48.2%, 44.0%, and 32.2%, respectively).

The rate of infections for the alemtuzumab 12 mg/day group was 1.051 per person-year. Further, the annualized rate of infections for the alemtuzumab 12 mg/day dose group did not increase with increasing number of cycles. The rate of infection was 1.244, 0.977, and 0.887 per person-year for Cycles 1, 2, and 3, respectively.

As with the overall risk of infection, the risk of serious infection also decreased over time. Cumulatively, the incidence of serious infection was lower in Years 2 through 4 compared with Year 1 for the alemtuzumab 12 mg/day dose group and the rate of serious infection did not increase with cycle number.

Opportunistic Infections

No events suggestive of significant or prolonged immunocompromise were reported in alemtuzumab-treated patients. Four alemtuzumab-treated patients had a tuberculosis (TB) infection. Of these, 2 were active cases of pulmonary TB, one bilateral, in patients from endemic regions (Ukraine and Russia). Two were cases of latent TB, one patient was noted to have a reactive tuberculin skin test on the day of the first infusion, having had the screening test planted two days earlier. No reactivation of TB infection was observed in 2 patients with latent TB that were treated with alemtuzumab. All 4 cases occurred in the first 2 years of follow-up and patients received anti-infective therapy according to local guidelines with full recovery. There was also one case of renal TB reported in a Rebif-treated patient.

Symptomatic CMV disease in immunocompromised individuals usually results in pneumonia, hepatitis, encephalitis, myelitis, colitis and retinitis. No such AEs were reported in alemtuzumab-treated patients. There was one event of CMV reported in the alemtuzumab studies which involved a non-serious, Grade 2 mononucleosis-like infection (sore throat, chills, and fever) in a single patient who responded to treatment.

In the active-controlled studies, localized fungal infections were reported more frequently in alemtuzumab-treated patients than in Rebif treated patients (12.1% versus 3.6%, respectively). None of the fungal infections were systemic and the most commonly reported events ($\geq$ 2% of patients) in both the alemtuzumab 12 mg/day and Rebif groups were similar: oral candidiasis and vulvovaginal candidiasis. Oral candidiasis was reported for 2.5% of patients receiving 12 mg alemtuzumab. Vulvovaginal candidiasis was reported for 3.3% of alemtuzumab 12 mg patients.

Such events are common among healthy, adult women and are not necessarily associated with immune incompetence, and thus does not imply treatment-associated immune suppression. Two patients (0.2%) experienced events of esophageal candidiasis; one had Grade 2 non-serious event and the second had Grade 3 infection of the distal esophagus that was reported as an SAE and resolved after the treatment with antifungal medication.

Finally, there were no reports of more serious opportunistic infections such as hepatitis C, progressive multifocal leukoencephalopathy, toxoplasmosis, or P. jiroveci.

Analysis of Infections by Use of Supplemental Systemic Steroids

Intermittent treatment with methylprednisolone is part of the management of MS as a symptomatic treatment for relapses. Supplemental systemic steroid use was associated with an increase in the rate of infection in both alemtuzumab and Rebif treated patients, without a disproportionate increase in association with alemtuzumab use. In the alemtuzumab 12 mg/day group, the rate of infections was 1.029 per person-year for patients who never received supplemental systemic steroids, 1.462 per person-year within 3 months following use of systemic steroids and 1.454 per person-year in patients >3 months following use of systemic steroids. For the Rebif group the rate of infection was 0.531, 0.750, and 0.774 per person-year, respectively.

Herpetic infections

Herpetic infections, primarily oral herpes simplex, were reported more frequently in alemtuzumab-treated patients (Table 33).

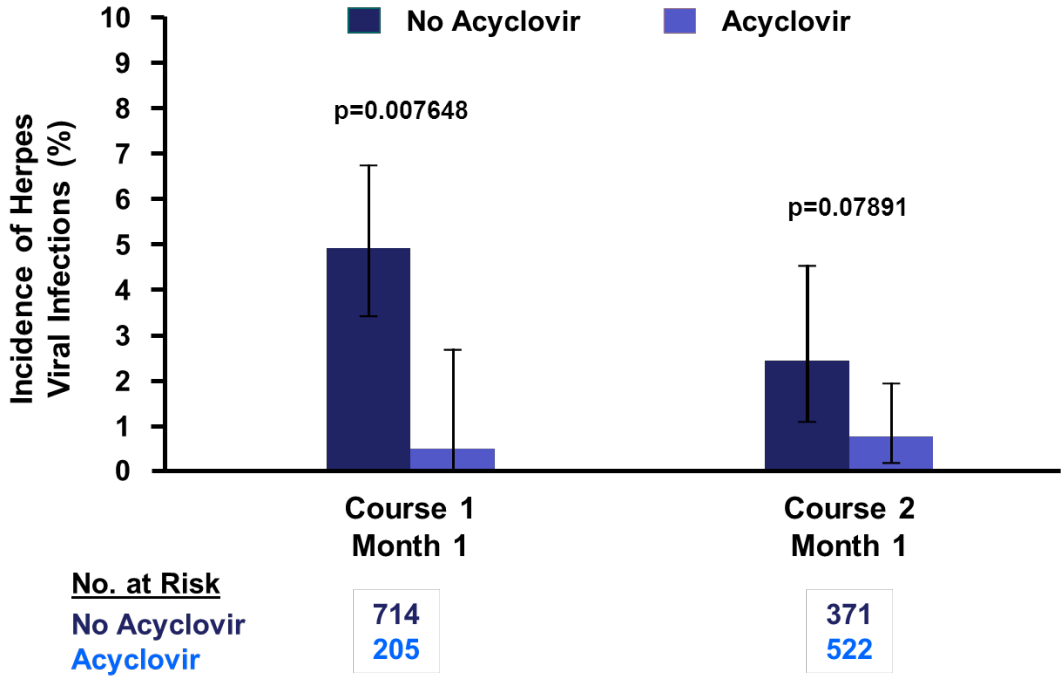
Table 33: Incidence of Herpes Viral Infections in the Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg/day (N=1486)
Preferred Term	**n (%)**	**n (%)**	**n (%)**
Herpes Viral Infections	15 (3.0)	144 (15.7)	295 (19.9)
Oral herpes	7 (1.4)	81 (8.8)	134 (9.0)
Herpes zoster	4 (0.8)	39 (4.2)	121 (8.1)
Herpes simplex	2 (0.4)	17 (1.8)	28 (1.9)
Genital herpes	1 (0.2)	12 (1.3)	22 (1.5)
Varicella	0 (0.0)	5 (0.5)	12 (0.8)
Herpes virus infection	1 (0.2)	2 (0.2)	8 (0.5)

Table 33: Incidence of Herpes Viral Infections in the Alemtuzumab Clinical Studies			
	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg/day (N=1486)
Herpes dermatitis	0 (0.0)	1 (0.1)	1 (0.1)
Herpes ophthalmic	0 (0.0)	0 (0.0)	2 (0.1)
Herpes simplex ophthalmic	0 (0.0)	1 (0.1)	1 (0.1)
Herpes zoster infection neurological	0 (0.0)	0 (0.0)	1 (0.1)
Herpes zoster multi-dermatomal	0 (0.0)	1 (0.1)	1 (0.1)
Meningitis herpes	0 (0.0)	1 (0.1)	1 (0.1)
Pneumonia herpes vital	0 (0.0)	1 (0.1)	1 (0.1)

Given this observation, the safety monitoring committee for the alemtuzumab studies recommended 1 month of treatment with acyclovir post alemtuzumab infusion. This was initiated early in the Phase 3 program but late enough to allow a comparison between those patients that received acyclovir prophylaxis and those that did not Figure 23. A total of 22.3% patients in Cycle 1 and 58.5% patients in Cycle 2 received prophylactic acyclovir (200 mg twice daily beginning on the first day of any alemtuzumab treatment cycle and continuing for 28 days following the last infusion day of any cycle). Acyclovir was effective in reducing the incidence of herpes infections during the first month of each course of treatment. Based on this observation, a recommendation for acyclovir prophylaxis during alemtuzumab treatment was included under the risk management plan.

Figure 23: Herpes Viral infections by Acyclovir Prophylaxis in the Alemtuzumab 12 mg/day Group, All Active-Controlled Studies (2 cycles)



Incidence is based on the number of alemtuzumab patients at risk in the corresponding time period. Acyclovir prophylaxis refers to acyclovir administration initiated on the first day of alemtuzumab treatment and continuing for a minimum of 1 month following each course of treatment.

Human Papillomavirus Infections

Human papillomavirus (HPV) infections were reported for 2.4% of patients in the alemtuzumab 12 mg/day group and 1.4% in the Rebif group in the active controlled experience but these did not appear to lead to an increased risk of cervical pathology as the incidence of cervical dysplasia was similar in both treatment groups (1.1% and 1%, respectively). Nevertheless, given the higher incidence of HPV infection Genzyme is proposing routine screening for HPV infection in women treated with alemtuzumab as part of the risk management plan.

5.1.8.3 Autoimmunity

Treatment with alemtuzumab may increase the risk of autoimmune conditions, particularly antibody-mediated autoimmunity, including thyroid disorders, ITP, or rarely, glomerular nephropathies (e.g., anti-GBM disease). The mechanisms underlying the increased risk have not been established. Occurrence of autoimmunity has been observed in other settings of immune reconstitution in lymphocytopenic patients (Gilquin, 1998, *Lancet*; Hsiao, 2001, *Bone Marrow Transplant*; Krupica, 2006, *Clin Immunol*), and MS patients have an increased background risk

for development of other autoimmune diseases (De Keyser, 1988, *Neurology*; Kirby, 2005, *Mult Scler*).

Although efforts have been made by Genzyme to explore pre-disposing factors which might allow the screening of patients at risk for an autoimmune disorder, no appropriate measure has yet been determined. However, Genzyme implemented a developmental risk minimization program in the Phase 2 and 3 studies to help in the timely recognition, diagnosis and management of autoimmune disorders arising after alemtuzumab. This program included educational measures for both treating physicians and patients in recognizing signs and symptoms of thyroid disease, ITP and anti-GBM disease, as well as surveillance measures including patient symptom surveys and monthly complete blood counts (CBCs) for ITP, monthly urinalysis and serum creatinine monitoring for nephropathies such as anti-GBM disease, and quarterly thyroid function testing.

Thyroid Disorders

Literature evidence points to a higher rate of thyroid disorders in the MS population (Horton, 2010, *Neuroepidemiology*, Niederwieser, 2003, *J Neurol*). Autoimmune thyroid abnormalities (particularly Grave's disease) were observed in pilot studies of alemtuzumab in MS patients (Coles, 1999, *Lancet*; Coles, 2006, *J Neurol*). Therefore, thyroid function was monitored on a quarterly basis in the Genzyme-sponsored clinical studies of alemtuzumab in MS patients, and a detailed assessment of both thyroid AEs and laboratory abnormalities was conducted.

In the active-controlled experience, the incidence of thyroid AEs was higher in the alemtuzumab 12 mg/day group (18.3%) than in the IFNB 1a group (5.4%) as was the rate of events (0.122 per person-year vs. 0.034 per person-year for alemtuzumab 12 mg/day and IFNB 1a, respectively; Table 34).

In all alemtuzumab-treated patients (complete follow up; Pool C), thyroid AEs were observed in 29.3%. The rate of thyroid AEs over all available follow up was 0.140 per person-year for the alemtuzumab pooled dose group.

Table 34: Incidence of Thyroid Adverse Events in Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Adverse events	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg (N=919)**	**Alemtuzumab 12 mg + 24 mg (N=1486)**
AEs, n (%)	27 (5.4)	168 (18.3)	435 (29.3)
Grade 1	23 (4.6)	83 (9.0)	192 (12.9)
Grade 2	5 (1.0)	93 (10.1)	305 (20.5)
Grade 3	0	10 (1.1)	40 (2.7)
Grade 4	0	1 (0.1)	2 (0.1)
SAEs, n (%)	0	7 (0.8)	26 (2.1)
Thyroid AEs leading to treatment discontinuation	1 (0.2)	3 (0.3)	3 (0.2)
Rate of thyroid AEs	0.034	0.122	0.140

In the active controlled studies, the most frequently reported thyroid AEs were hypothyroidism, hyperthyroidism, and Graves' disease respectively (Table 35). Hypothyroidism and hyperthyroidism occurred at a similar incidence (5.0% and 4.1% of patients, respectively) in the alemtuzumab 12 mg group. Thyroid AEs led to discontinuation of treatment in 3 alemtuzumab-treated patients (12 mg/day group only) and 1 Rebif-treated patient.

Table 35: Thyroid Adverse Events Reported in 5% of Patients in Any Treatment Group in the Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Preferred Term	**IFNB-1a (N=496)**	**Alemtuzumab 12 mg (N=919)**	**Alemtuzumab 12 mg + 24 mg (N=1486)**
Any Event	27 (5.4)	168 (18.3)	435 (29.3)
Hypothyroidism	8 (1.6)	46 (5.0)	139 (9.4)
Hyperthyroidism	4 (0.8)	38 (4.1)	141 (9.5)
Graves' disease	0 (0.0)	29 (3.2)	110 (7.4)

Thyroid function test abnormalities (abnormal TSH and abnormal free T4) were also reported more frequently in the alemtuzumab 12 mg/day group than in the IFNB-1a group. When the 2 definitions of thyroid disorders were combined, defining a thyroid disorder as a reported thyroid AE or a thyroid laboratory abnormality (i.e., abnormal TSH with simultaneous abnormal free T4), the incidence of thyroid disorders was still higher in the alemtuzumab 12 mg/day group, but a significant number of events were detected in Rebif treated patients in the active controlled studies (38.6% vs. 28.2%, respectively, Table 36).

Table 36: Incidence of Treatment-Emergent Thyroid Laboratory Abnormalities in the Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 12 + 24 mg (N=1486)
Thyroid abnormality	**n (%)**	**n (%)**	**n (%)**
Abnormal TSH	115 (23.4)	302 (32.9)	595 (40.0)
Abnormal FT4	46 (9.6)	202 (22.5)	477 (38.9)
Any thyroid lab abnormality (defined as abnormal TSH or FT4)	139 (28.3)	344 (37.4)	647 (43.5)
Any thyroid lab abnormality or thyroid AE	140 (28.2)	355 (38.6)	661 (44.5)
Any thyroid lab abnormality and thyroid AE	26 (5.3)	157 (17.1)	421 (28.3)

Thyroid AEs refer to AEs coded to MedDRA HLGT 'Thyroid gland disorders', or coded to HLT 'Thyroid analyses', 'Thyroid radiotherapies', 'Thyroid therapeutic procedures', 'Thyroid histopathology procedures', or coded to PT 'Blood thyroid stimulating hormone abnormal', 'Blood thyroid stimulating hormone increased', 'Blood thyroid stimulating hormone decreased'.
TSH = Thyroid Stimulating Hormone; FT4 = Free levothyroxine.

In all alemtuzumab-treated patients (complete follow up; Pool C) the annual incidence of thyroid AEs was 5.0% in Year 1, 9.2% in Year 2, 17.4% in Year 3, and 8.9% in Year 4 in the alemtuzumab 12 mg/day group.

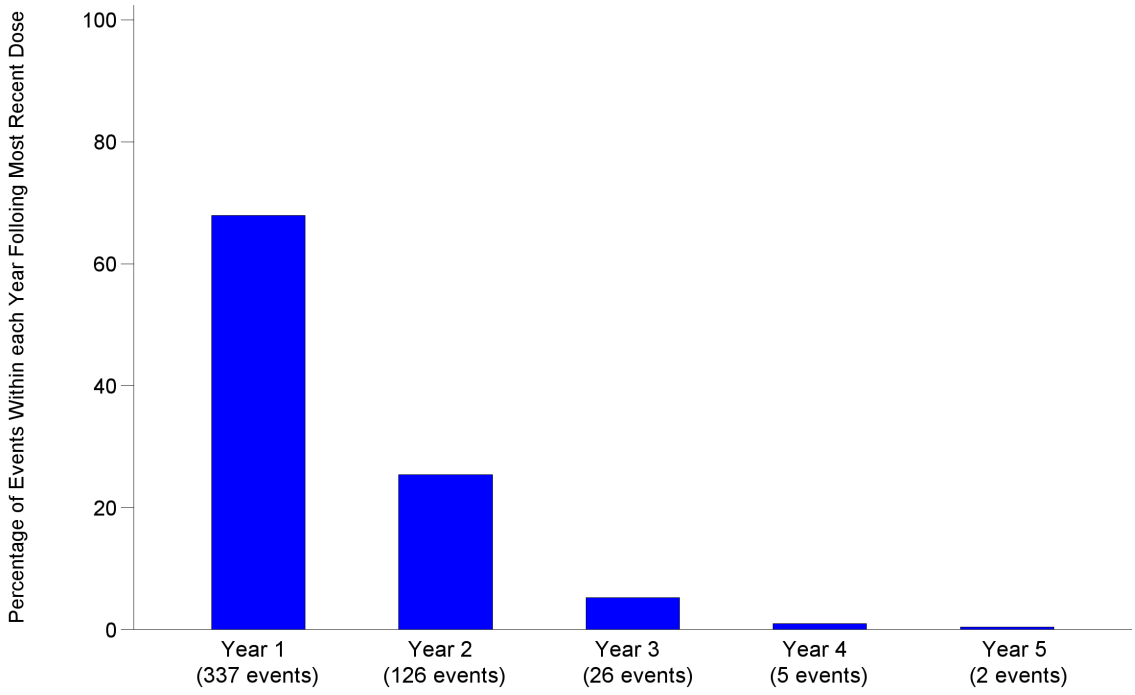
In all alemtuzumab-treated patients (complete follow up; Pool C), thyroid AEs were observed in 35.2% of patients treated with alemtuzumab 12 mg/day and 35.1% for the alemtuzumab pooled dose group (12 mg/day and 24 mg/day) through 4 years.

Detection and Treatment

Thyroid AEs were detected through quarterly monitoring of TSH or through education based recognition of signs and symptoms of hypo- and hyperthryroidism. Once diagnosed, most thyroid events were managed with conventional oral medications (66.2%) or required no medical therapy (22.5%). Eighteen patients (4.1%) were treated surgically (Table 37).

When assessing the time of onset of thyroid events relative to most recent alemtuzumab infusion, an analysis found that 94% of first events occurred within 2 years following the most recent alemtuzumab dose (Figure 24) and only two events occurred more than 48 months after the last dose of alemtuzumab. Since routine thyroid function monitoring was useful in identifying potential adverse events in the clinical program, quarterly thyroid monitoring is proposed under the risk management plan for alemtuzumab for a period of 4 years as this should provide an adequate duration to detect the onset of possible thyroid disorders associated with use of alemtuzumab.

Figure 24: Patients with Thyroid Abnormalities: Occurrence of First Thyroid Abnormality in Each Yearly Interval Following Most Recent Alemtuzumab Dose



Thyroid abnormality defined as any thyroid stimulating hormone (TSH) laboratory abnormality or adverse event under the MedDRA HLGTs 'Thyroid gland disorders', or coded to HLT 'Thyroid analyses', Thyroid radiotherapies', 'Thyroid therapeutic procedures', 'Thyroid histopathology procedures', or coded to PT 'Blood thyroid stimulating hormone abnormal', 'Blood thyroid stimulating hormone increased', 'Blood thyroid stimulating hormone decreased'.

Table 37: Thyroid Adverse Events, Treatments and Outcomes through All Available Follow-up (Pool C)

Adverse events	**Alemtuzumab 12 mg + 24 mg (N=1486)**
AEs, n (%)	435 (29.3)
Treated with conventional oral medications	288 (66.2)
Treated with iodine ablation	31 (7.1)
Treated surgically	18 (4.1)
Did not require treatment	98 (22.5)

Seriousness and severity

In the active-controlled studies, the majority of thyroid AEs (94.1%) in the alemtuzumab 12 mg/day group were mild or moderate in severity. Thyroid AEs led to discontinuation of treatment in 3 (0.3%) alemtuzumab-treated patients (12 mg/day group) and 1 Rebif-treated patient.

Serious thyroid AEs over 3 years of follow up in the active-controlled studies were reported in 7 (0.8%) patients in the alemtuzumab 12 mg/day group; no serious thyroid AEs were reported in the Rebif group. Of the serious cases, one patient developed Grave's disease during pregnancy leading to neonatal Graves' disease and Grade 4 thyrotoxicosis in the newborn. She received Cycle 2 two months after delivery and experienced two subsequent thyroid SAEs: thyrotoxic crisis (Grade 3) and endocrine ophthalmopathy (Grade 2) that occurred 23 months after start of alemtuzumab treatment. The patient and infant received treatment and fully recovered.

Serious thyroid AEs were reported in 2.3% of patients in the alemtuzumab pooled dose group in over all available follow-up. The incidence of serious thyroid AEs was in Years 2 and 3 (0.5% and 1.4%, respectively) were higher than in Year 1 (0.2%). Overall, 34 serious thyroid AEs were reported in the alemtuzumab 12 mg/day group (2.3%). The serious thyroid events with the highest incidence in the alemtuzumab 12 mg/day group (≥ 0.2%) were Graves' disease (1.4%), hyperthyroidism (0.6%), and hypothyroidism (0.2%).

Immune Thrombocytopenic Purpura (ITP)

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (platelet count <100 x 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. The diagnosis is one of exclusion as there currently is no robust clinical or laboratory parameter available for accurate diagnosis (Rodeghiero, 2009, *Blood*). The age-adjusted prevalence of ITP in the US has been estimated at 9.5 per 100,000 persons among the general population, although there are little data available (Segal, 2006, *J Thromb Haemost*).

Following the diagnosis of the fatal index case in the Phase 2 study (CAMMS223) that led to suspension of alemtuzumab dosing, a safety monitoring program was implemented in the alemtuzumab clinical studies. This program included close monitoring for signs of ITP through patient and investigator education, monthly CBCs with platelet counts, and a monthly patient questionnaire about symptoms possibly indicative of severe thrombocytopenia, offset by 2 weeks from the laboratory testing. A protocol definition of ITP was specified to guide investigators during the conduct of the studies. This definition was based upon commonly employed diagnostic criteria for ITP. Patients were discontinued from further alemtuzumab treatment once ITP was diagnosed. Importantly, monitoring for signs and symptoms of ITP is an integral part of the risk mitigation strategy for alemtuzumab and part of the required training specified in the restricted distribution program (see Section 7.2).

In order to comprehensively analyze all potential ITP cases, events were identified in the database based upon whether particular AE preferred terms were indicated by the investigator (e.g. immune thrombocytopenia) and by a broader platelet-based definition that identified cases with platelet values below a pre-defined threshold based upon accepted diagnostic criteria (platelet count <100 x 10^9/L). Identified cases were then medically reviewed applying the clinical criteria required to confirm diagnosis.

In all active-controlled studies (Pool E), a total of 24 patients in any treatment group met the AE-based or platelet-based definitions for ITP over 3 years of follow up: 16 alemtuzumab-treated patients (9 treated with alemtuzumab 12 mg/day and 7 treated with alemtuzumab 24 mg/day) and 8 (1.6%) Rebif treated patients with an annualized rate of 0.0062 and 0.0080 per person-year, respectively (Table 38).

Table 38: Incidence and Rate of First Immune Thrombocytopenic Purpura in 3-Year Active-Controlled Experience (Pool E)

	IFNB-1a (N=496)		Alemtuzumab 12 mg/day (N=919)		Alemtuzumab Pooled (N=1188)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Platelet-based definition	8 (1.6)		9 (1.0)		14 (1.2)	
AE-based definition	2 (0.4)		8 (0.9)		14 (1.2)	
Autoimmune thrombocytopenia	0		6 (0.7)		9 (0.8)	
Idiopathic thrombocytopenic purpura	2 (0.4)		2 (0.2)		5 (0.4)	
Platelet-based or AE-based definition	8 (1.6)	0.0080	9 (1.0)	0.0047	16 (1.3)	0.0062

Percentages are based on the number of treated patients in the corresponding treatment group.
Rates are based on the total number of person-years in the corresponding column. An individual patient's contribution to the total number of person-years is censored at the time of the event.
Platelet-based definition: Platelet count ≤ 100 x 10^9/L on ≥ 2 occasions over a period of at least 30 days with no platelet counts above the LLN during the 30 day period or platelet count ≤50 x 10^9/L on ≥ 2 occasions over any time period with no platelet counts above the LLN in the period between the 2 platelet counts ≤ 50 x 10^9/L.
AE-based definition: AEs with PT of Autoimmune thrombocytopenia, Idiopathic thrombocytopenic purpura, or Thrombocytopenic purpura.

Through all available follow-up, a total of 27 patients of the 1486 (1.8%) alemtuzumab-treated patients met the AE-based or platelet-based definitions for ITP, for an overall annualized rate of 0.0051 per person-year. Of the 27 cases, 16 were SAEs.

Table 39: Incidence and Annualized Rate of First Treatment-Emergent Immune Thrombocytopenic Purpura - All Available Follow-up (Pool C)

	Alemtuzumab 12 mg/day (N=1217)		Alemtuzumab 24 mg/day (N=269)		Alemtuzumab Pooled (N=1486)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Platelet-based or AE-based definition	17 (1.4)	0.0042	10 (3.7)	0.0080	27 (1.8)	0.0051
Platelet-based definition	15 (1.2)		8 (3.0)		23 (1.5)	
AE-based definition	12 (1.0)		9 (3.3)		21 (1.4)	
Autoimmune thrombocytopenia	8 (0.7)		4 (1.5)		12 (0.8)	
Idiopathic thrombocytopenic purpura	4 (0.3)		5 (1.9)		9 (0.6)	

Percentages are based on the number of treated patients in the corresponding treatment group.
Rates are based on the total number of person-years in the corresponding column. An individual patient's contribution to the total number of person-years is censored at the time of the event.
Platelet-based definition: Platelet count ≤ 100 x 109/L on ≥ 2 occasions over a period of at least 30 days with no platelet counts above the LLN during the 30 day period, or platelet count ≤ 50 x 109/L on ≥ 2 occasions over any time period with no platelet counts above the LLN in the period between the 2 platelet counts ≤ 50 x 109/L.
AE-based definition: AEs with PT of 'Autoimmune thrombocytopenia', 'Idiopathic thrombocytopenic purpura' or 'Thrombocytopenic purpura'.

Cases identified by AE and/or platelet criteria were then reviewed applying widely used international criteria (Rodeghiero, 2009, *Blood*; Provan, 2010, *Blood*) for ITP diagnosis.

The cases were classified into 2 groups:

1.) Confirmed ITP with no alternative etiology and likely related to treatment (21 cases):

2.) Cases which were not consistent with ITP or have ITP attributed to other causes (6 cases):

- Patient 111-1067: ITP in the setting of H. pylori infection, responded to antibiotic treatment
- Patient 7102-5804: ITP after a gastrointestinal illness with serology suggestive of Coxsackie b infection.
- Patient 104-1171: Low platelet count due to artifact (platelet aggregation) documented in CAMMS223 study.
- Patient 202-1016: Thrombocytopenia was documented at study entry, prior to alemtuzumab treatment. Platelet counts were intermittently low throughout study participation, without clinical consequence.
- Patient 305-1191: Grade 1 thrombocytopenia was observed coincident with initiation of Betaferon treatment three years after the last dose of alemtuzumab. This case was assessed as related to Betaferon by the Investigator.
- Patient 7105-3488: Alternative diagnosis: Pancytopenia; after initial recovery the patient did not comply with treatment and had a relapse with concomitant sepsis that had a fatal outcome (See Section 5.1.7).

Treatment and Response to Treatment for the Confirmed ITP Cases

Of the 21 medically confirmed ITP cases as described above, with the exception of the index fatal case, all cases were detected through the monitoring program, either by the monthly platelet counts or the early recognition of signs and symptoms. Most patients achieved prompt platelet count response (within 3 months of diagnosis after treatment with an ITP) with first-line therapy, i.e., corticosteroids and/or IVIG with or without adjuvant platelet transfusion. Four patients received additional second-line therapies (e.g., Rituximab, Danazol), and 1 patient recovered

spontaneously without treatment. One patient (Patient 3006-5807) underwent splenectomy for treatment of ITP.

Other Autoimmune Cytopenias

There were 2 SAEs of pancytopenia that were reported through all available follow up in the alemtuzumab 12 mg/day group. One case was the reported event of autoimmune pancytopenia with fatal outcome (refer to Section 5.1.7). The second SAE was not reported as autoimmune, though it occurred in a patient that had previously reported events of autoimmune hemolytic anemia and ITP.

During all available follow up, 2 (0.1%) patients in the alemtuzumab 12 mg/day group had an AE of autoimmune hemolytic anemia.

Autoimmune neutropenia was not reported in the MS clinical program.

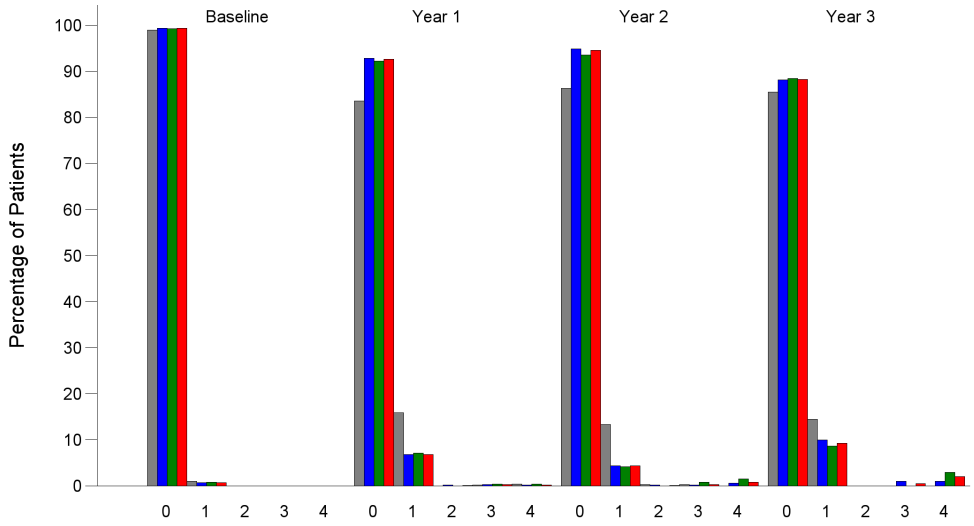
Monitoring of Complete Blood Counts

To further assess for the potential impact of alemtuzumab on haematological parameters complete blood counts were reviewed across the entire study population.

Platelets

In all active-controlled studies (Pool E), mean platelet counts decreased from baseline in all treatment groups at Month 1 but the mean platelet count for Rebif patients decreased below that observed for alemtuzumab-treated patients at Month 2 and remained lower than alemtuzumab throughout 3 year follow up. Shift analyses of change in platelet counts from baseline to Year 1 and Year 2 were consistent with these results: post-baseline shifts to below normal were reported in a larger percentage of Rebif patients than alemtuzumab 12 mg/day patients (15.6% versus 6.7% in Year 1; 13.4% versus 4.9% in Year 2). Post baseline shifts to below normal were reported for the same percentage of Rebif and alemtuzumab 12 mg/day patients in Year 3 (11.1%). Most patients with low platelet counts had values of Grade 1 in severity (75-150 x 10^9/L) in Years 1 through 3(Figure 25).

Figure 25: CTC Grade for Platelet Count at Baseline and Worst (Lowest) Post-Baseline Value by Year in 3-Year Active-Controlled Experience (Pool E)



No. of Patients																				
SC IFNB-1a	490	5	0	0	0	411	78	0	1	2	390	60	1	1	0	65	11	0	0	0
Alem 12 mg/day	912	6	0	0	0	853	62	1	2	1	866	40	1	1	5	89	10	0	1	1
Alem 24 mg/day	267	2	0	0	0	248	19	0	1	1	248	11	0	2	4	92	9	0	0	3
Alem Pooled	1179	8	0	0	0	1101	81	1	3	2	1114	51	1	3	9	181	19	0	1	4

Note: Percentages are based on the number of patients with data during the corresponding time period in each treatment group. A patient is counted only once in the worst grade within the corresponding time period.
Note: CTC Grade Ranges in 10^9/L: 0: ≥ LLN; 1: ≥75 - <LLN; 2: ≥50 - <75; 3: ≥ 25 - <50; 4: <25
CTC = Common Toxicity Criteria.

There was no apparent increase in the percentage of patients with low platelet counts or the severity of low platelet counts with continued follow-up or increasing numbers of alemtuzumab cycles received.

Hemoglobin

In all active-controlled studies (Pool E), during the first few months of treatment, the mean hemoglobin values decreased in all treatment groups. The mean hemoglobin values for alemtuzumab 12 mg/day patients were below those for Rebif patients at Month 1, but recovered to baseline levels by Month 3 and remained higher than the mean values for Rebif patients throughout 3 years of follow up.

Post baseline shifts to below normal were reported for more Rebif patients than alemtuzumab 12 mg/day patients in Year 1 and Year 2 (33.6% versus 26.6% in Year 1; 33.3% versus 22.5% in Year 2). The percentages were similar in Year 3 (22.9% versus 20.8%, alemtuzumab 12mg versus Rebif, respectively).

Neutrophils

In the active controlled studies (3 years of follow up; Pool E), the mean neutrophil counts in all treatment groups decreased at Month 1, but the mean neutrophil count for alemtuzumab patients had increased by Month 2 while the counts in the Rebif group remained low throughout the 3-year follow up. Shift analyses of change from baseline in ANC were consistent with these results: more Rebif patients experienced post-baseline shifts to below normal values than alemtuzumab 12 mg/day patients (39.2% versus 17.1% in Year 1; 35.5% versus 14.5% in Year 2; 35.2% versus 25.6% in Year 3).

Nephropathies

Glomerular nephropathies are a group of diseases that generally cause inflammation of the kidney glomerulus; the etiology and pathogenesis between these nephropathies differ but clinical manifestations are similar and may include hematuria, proteinuria, and decrease in glomerular filtration rate (GFR).

Alemtuzumab has been associated with glomerulonephritis in patients with MS. Anti-glomerular basement membrane (anti-GBM) disease was reported in 1 MS patient who received alemtuzumab in an investigator-sponsored study and was identified in 1 patient in the Phase 2 study of alemtuzumab (CAMMS223); therefore, an analysis of nephropathies (including anti-GBM disease) was performed for the entire alemtuzumab clinical program.

In all alemtuzumab-treated patients (complete follow up; Pool C), 4 events of glomerular nephropathy were identified for 4 (0.3%) patients in the 12 mg/day alemtuzumab dose group (no additional cases reported in the 24 mg/day group) with a rate of 0.00084 per person-year. Events occurred within 39 months following the last administration of alemtuzumab. These 4 cases were reported as: glomerulonephritis membranous (2), anti-GBM glomerulonephritis (1) and Goodpasture's syndrome (1).

- Patient 122-1319 was a 35-year-old White female who received 2 cycles of alemtuzumab 12 mg/day. At Month 39 following the last dose of alemtuzumab, laboratory monitoring revealed elevated urea, creatinine, and C-reactive protein. Renal biopsy revealed necrotizing and crescentic glomerulonephritis consistent with anti-GBM disease, reported as a Grade 3 SAE of Goodpasture's syndrome. Serum anti-GBM antibody tests were negative. The patient was hospitalized for treatment that included plasmapheresis,

cyclophosphamide and prednisone, leading to durable improvement in renal function. The patient's nephrologist noted during a follow-up visit that anti-GBM disease was in remission. The case was assessed as related to alemtuzumab.

- Patient 7001-1041, a 58-year-old white female who had received 2 cycles of alemtuzumab 12 mg/day, developed grade 2 nephrotic syndrome approximately 13 months after her last dose of alemtuzumab. The patient presented with leg edema, lab results showed a creatinine level of 67 µmol/L, and urine was positive for blood and protein. The diagnosis derived, in part, from additional findings from immunofluorescence and electron microscopy was severe angionephrosclerosis combined with stage II membrane glomerulonephritis. The patient was treated initially with diuretics and albumin and continued to be treated with diuretics only. The most recent laboratory values showed creatinine 80 µmol/L and proteinuria (3+). The patient continues to be enrolled in the Extension Study CAMMS03409.

- Patient 6004-3087 was a 25-year-old White female who received 3 cycles of alemtuzumab 12 mg/day. At Month 4 following the last dose of alemtuzumab, periodic urinalysis results were positive for blood and protein and the patient subsequently developed nephrotic syndrome with proteinuria and hypoproteinemia. Renal biopsy showed membranous nephropathy, and increasing levels of anti-GBM antibodies were also reported. The patient was initially treated with angiotensin-converting enzyme (ACE) inhibitors without improvement. The case progressed from Grade 1 to Grade 3 in severity. After further deterioration of renal function, steroids, cyclophosphamide, and plasmapheresis were initiated, which led to reduction in proteinuria (1+) and to normalization of anti-GBM titer. The diagnosis was changed from membranous nephropathy to anti-GBM glomerulonephritis during the course of the condition, and was assessed as an SAE and related to alemtuzumab. This patient is still receiving low dose oral steroids (5 mg/day) and oral cyclophosphamide (50 mg/day) and has improved renal function.

- Patient 1008-6030 was a 26-year-old woman who received 2 cycles of alemtuzumab 12 mg/day. At Month 5, following the last alemtuzumab cycle, the patient developed non-serious Grade 3 membranous glomerulonephritis. During monthly laboratory testing, the patient was noted to have proteinuria and microhematuria with normal creatinine. Later, the patient reported bilateral ankle edema and weight gain. Further assessments revealed a negative anti-GBM antibody test, and ultrasound showed normal-sized kidneys and no

obstruction. A kidney biopsy showed stage 1 to 2 membranous glomerulopathy. The Investigator assessed the event as related to alemtuzumab and the patient was treated with furosemide and lisinopril, with improvement of her symptoms.

The 4 cases of glomerular disease were identified early through the risk monitoring plan established during the clinical program; 1 case was identified through abnormal monthly serum creatinine, 2 through identification of hematuria and proteinuria on monthly urinalysis and 1 case through the patient recognition and reporting of signs and symptoms (awareness/education). These patients responded to timely medical treatment and did not develop permanent kidney failure.

As clinical manifestations of anti-GBM disease may include serum creatinine, hematuria, and/or proteinuria, the occurrence of these events was examined. In addition, the incidence of hematuria and proteinuria AEs was examined. Over all available follow up, the incidence of hematuria or proteinuria AEs in the alemtuzumab 12 mg/day group was 4.1% and 5.3%, respectively.

Renal Function

In the active-controlled studies (Pool E), mean serum creatinine values were generally lower and fluctuated more in the Rebif group than in the alemtuzumab group, but remained within the normal range for all treatment groups during 3-year follow up.

Grade 2 values (>1.5 - 3.0 x ULN) were reported for 2 alemtuzumab 12 mg/day patients during Year 1, 3 alemtuzumab 12 mg/day patients during Year 2, and 0 alemtuzumab 12 mg/day patients during Year 3 of the active-controlled studies. Grade 3 values (>3.0 - 6.0 x ULN) were reported for 2 alemtuzumab 12 mg/day patients during Year 1. However, in all cases the next serum creatinine measurement (repeated measurement or next monthly assessment) after the Grade 2 or Grade 3 values was within normal limits. No shifts from baseline to Grade 3 or 4 values for serum creatinine were observed in the Rebif group.

During all available follow-up in all alemtuzumab treated patients (Pool C), the frequency of Grade 2 or higher severity of creatinine values for patients treated with alemtuzumab 12 mg/day remained low (<0.7%), and there was no apparent increase in the severity of creatinine elevations with the number of alemtuzumab cycles received.

5.1.8.4 Malignancies

The overall incidence and rate of malignancies reported in the active controlled experience and during all available follow-up presented in Table 40. The most common malignancies observed

in Pool C (all alemtuzumab-treated patients, all available follow-up) were thyroid cancer, breast cancer and basal cell carcinoma. The rate of these malignancies in alemtuzumab-treated patients is in line with the rate of the most frequently reported cancers in white, young adults.

Table 40: Incidence of Malignancies in the Alemtuzumab Clinical Studies

	3-Year Active Controlled Experience (Pool E)		All Available Follow Up (Pool C)
Preferred term	**Rebif N=496**	**Alemtuzumab 12 mg N=919**	**Alemtuzumab 12 mg + 24 mg N=1486**
Any malignancies, n (%)	**2 (0.4)**	**4 (0.4)**	**19 (1.3)**
Thyroid cancer	0 (0.0)	3 (0.3)	5 (0.3)
Breast cancer	0 (0.0)	0 (0.0)	5 (0.3)
Basal cell carcinoma	1 (0.2)	1 (0.1)	4 (0.3)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	2 (0.1)
Cervix carcinoma	0 (0.0)	0 (0.0)	1 (0.1)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.1)
Vulval cancer stage 0	0 (0.0)	0 (0.0)	1 (0.1)
Acute myeloid leukemia	1 (0.2)	0 (0.0)	0 (0.0)
Any event, rate per 100 Persons years (CI)	**0.289 (0.061, 0.870)**	**0.206 (0.056, 0.528)**	**0.349 (0.159, 0.662)**

All 5 thyroid malignancies occurred in patients who developed a thyroid disorder during the study and were discovered as incidental findings on ultrasound exam. Four of the 5 cases were microcarcinomas (per tumor size) and 2 of 5 patients had pre-existing nodules at Baseline.

No meaningful trends in malignancies were observed with respect to the incidence or rate of malignancies by number of treatment cycles, years of follow up, or cumulative alemtuzumab dose.

5.1.8.5 Reproduction and Lactation

There are no adequate and well-controlled studies of alemtuzumab in pregnant women, but pregnancies have been reported in clinical studies.

Contraception was required throughout the clinical studies, but pregnancies occurred during and following study participation. A total of 99 pregnancies in 78 alemtuzumab-treated patients have been reported in the MS clinical program as of 26 November 2012 (note this includes patients originally treated with Rebif who subsequently received alemtuzumab and became pregnant following alemtuzumab exposure). A description of pregnancy outcomes is provided in Table 41.

Table 41: Cumulative Pregnancy Experience for Alemtuzumab (MS Clinical Program)

	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	All Alemtuzumab Treated Patients
Pregnancy Outcome	75 pregnancies (61 pts)[a]	24 pregnancies (17 pts)	99 pregnancies (78 pts)[a]
Live Birth[c]	40[b, c]	11[d]	51[c]
Elective abortion[d]	8	3	11
Spontaneous abortion (<20 weeks)	14	6	20
Stillbirth (≥ 20 weeks)	1	0	1
Ongoing	8	2	10
Unknown	4	2	6

a Category includes 8 pregnancies in 8 patients who were originally treated with IFNB-1a who subsequently received alemtuzumab and became pregnant following alemtuzumab exposure. The breakdown of the 8 pregnancies was as follows: 2 full term, 1 elective abortion, 3 ongoing, 2 unknown.
b One patient was pregnant with twins and miscarried 1 baby, the other baby was delivered full term (data from Genzyme GPE Database)
c Category includes 2 pregnancies (2 pts) who delivered a preterm baby (defined as >32 weeks and ≤ 35 weeks)
d Of the elective abortions, one elective abortion each was due to fetal defects (cystic hygroma and hypoplastic heart, Patient 5501-5560), suspicion of extrauterine pregnancy, and anembryonic gestation; 6 elective abortions were due to patient's personal choice related to family, financial, or other unspecific reasons; and no information is available for the remaining 2 cases.

An optional substudy for male patients in studies CAMMS323 and CAMMS324 evaluated potential effects of alemtuzumab on human sperm. Participants provided two ejaculate samples, separated by at least 48 hours, at each time point. Of 13 alemtuzumab-treated patients in the semen substudy (12 mg, n=10; 24 mg, n=3), all had sperm concentration, sperm motility, and percentage of morphologically normal sperm within or above the range of baseline or normal values in ≥1 sample at each post-treatment time point. These limited data suggest alemtuzumab has no adverse impact on sperm quality, quantity, or motility.

5.1.9 Safety Conclusions

Adverse events more common on alemtuzumab generally fell into the categories of those events associated with infusions, infections, and autoimmune disease, areas previously identified as potential risks of alemtuzumab treatment from both the B-CLL experience with Campath and the pilot studies performed in MS patients. There has been a consistent pattern of safety considerations that primarily include IARs, autoimmune disorders (thyroid disorders, ITP and nephropathies such as anti-GBM disease), and infections. Measures to detect and manage these effects were implemented early and refined throughout the clinical program.

Nearly all alemtuzumab-treated patients experienced IARs, but these events were most often mild or moderate in severity and generally did not prevent patients from completing scheduled alemtuzumab treatment cycles and remaining in the studies. One case of anaphylaxis was reported, but there were no events of severe cutaneous reactions, such as Stevens-Johnson syndrome. Prophylactic use of corticosteroids was useful in alleviating IARs.

Infections were common in both alemtuzumab and Rebif treatment groups, although alemtuzumab was associated with a higher risk. Infections were usually mild or moderate in severity, and responded to conventional management measures. Prophylactic acyclovir treatment was used effectively in the clinical studies to reduce risk of HSV and it is proposed that patients to be treated with alemtuzumab receive concomitant acyclovir starting on the first day of any alemtuzumab cycle and continuing for at least 1 month after the last day of the cycle.

Alemtuzumab treatment may increase the risk of autoimmune-mediated conditions. Observed autoimmune thyroid disorders included both hyperthyroidism and hypothyroidism, which occurred at similar rates. No consistent pattern was observed with regards to time of onset after treatment initiation, although the highest incidence of thyroid AEs was observed between 24 and 42 months after the first treatment cycle, and all but 1 event occurred within 48 months after last dose. Measurement of TSH at baseline and every 3 months allowed the detection and treatment of thyroid disorders in these patients.

ITP and glomerulonephritis were observed infrequently. Risk minimization measures (including monthly CBCs) introduced after the fatal index case of ITP in the Phase 2 study to monitor for ITP allowed diagnosis and treatment of patients who subsequently developed the condition. Similarly, the monthly frequency of serum creatinine testing was effective in identifying cases early to allow prompt treatment and is considered an appropriate monitoring tool by

nephrologists. Similarly, urinalysis testing was also effective in identifying a number of nephropathies during the clinical studies.

Malignancies were observed in both alemtuzumab- and Rebif-treated patients at annualized rates similar across all treatment groups, and moreover, the malignancy risk was similar to the background incidence in the general population.

6. Clinical Pharmacology and Immunogenicity

6.1.1 Clinical Pharmacology

Evaluations of alemtuzumab pharmacokinetics and pharmacodynamics in MS patients were conducted within the Phase 3 and Phase 2 studies using validated quantitative flow cytometry and immunoassay methods. A population pharmacokinetic and pharmacodynamic analysis was also conducted. Alemtuzumab is a recombinant humanized protein for which the expected metabolic pathway is proteolysis; therefore classical drug-drug interaction studies have been performed. There are no known clinically significant interactions of alemtuzumab with other drug products, foods, or other substances.

6.1.1.1 Pharmacokinetics

The pharmacokinetics of alemtuzumab were evaluated in a total of 216 patients (19 in CAMMS223, 57 in CAMMS323, and 140 in CAMMS324) with RRMS who received either 12 mg (157 patients) or 24 mg (59 patients) for 5 days, followed by a 3-day treatment cycle 12 months after the initial treatment cycle. The results of the Phase 2 and 3 studies showed consistent trends in alemtuzumab pharmacokinetics. Serum concentrations increased with each daily administration within a treatment cycle, with the highest observed concentrations occurring following the last dose. Cmax values were comparable between cycles. Administration of the recommended 12 mg dose resulted in a maximum serum concentration (Cmax) of 3014 ng/mL on Day 5 of the initial treatment cycle, and 2276 ng/mL on Day 3 of the second treatment cycle. Serum alemtuzumab concentrations were higher following administration of the 24 mg dose as compared with the 12 mg dose. Serum concentrations became low or undetectable within approximately 30 days (Month 1) following each treatment cycle with the 12 mg dose and within approximately 90 days (Month 3) following each treatment cycle with the 24 mg dose.

The population pharmacokinetics of alemtuzumab were best described by a linear, 2 compartment model.

Systemic clearance in MS patients decreased with lymphocyte count due to loss of CD52 antigen in the periphery; however, the decrease in clearance from initial to second treatment cycle was

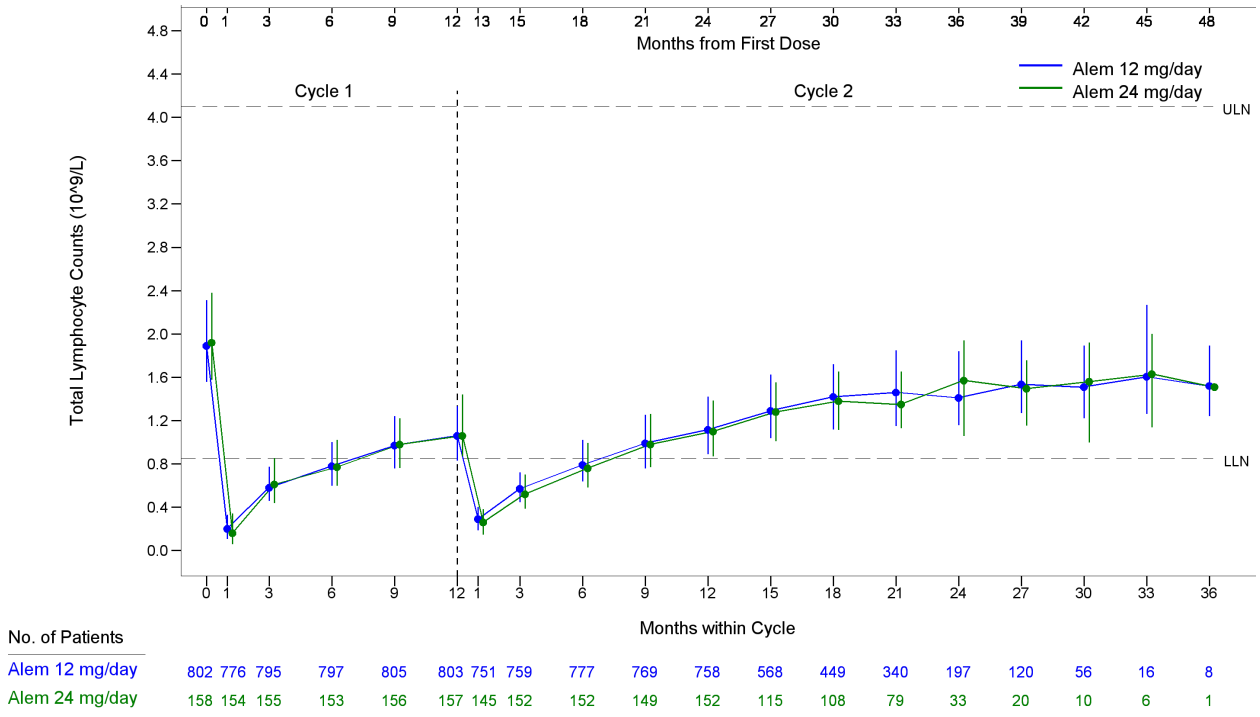
less than 20%, suggesting the influence of lymphocyte count on clearance was not clinically significant. The central volume of distribution was proportional to body weight, and approximated extracellular fluid volume (14.1 L), suggesting that alemtuzumab is largely confined to the blood and interstitial space, as could be expected for a relatively large molecule. The estimated alpha half-life of alemtuzumab approximates 2 days and appears to be independent of cycle (i.e., lymphocyte count), anti-alemtuzumab antibody status, and dose level.

No effect of age, race or gender on the PK of alemtuzumab was observed.

6.1.1.2 Pharmacodynamics

Clinical studies show lymphopenia and subsequent lymphocyte repopulation to be the primary pharmacodynamic effect of alemtuzumab in MS. Pharmacodynamics in the clinical studies were assessed by measurement of major T and B lymphocyte subsets and NK cells (CD3+, CD4+, CD8+, CD19+, CD16+56+) and absolute lymphocyte count. Alemtuzumab rapidly depleted circulating T and B cells after each treatment cycle with the lowest values typically occurring at the first post-treatment assessment, which was after 1 month in the Phase 3 studies (and as early as 2 days after the end of the first treatment cycle in the Phase 2 study). Lymphocyte repopulation appeared to occur at about the same rate after each treatment cycle (Figure 26), and the nadir and degree of repopulation following the second cycle was comparable to the first with no indication that alemtuzumab's effects on lymphocytes are cumulative. Similar patterns of lymphocyte depletion and repopulation were generally observed for the 24 mg dose groups as compared with the 12 mg dose groups (Figure 26). Overall, no apparent differences were noted between the 24 mg and 12 mg doses in the pharmacodynamic response as measured in peripheral blood, despite the expectedly higher serum concentrations of alemtuzumab observed after administration of the 24 mg dose.

Figure 26: Median Total Lymphocyte Counts Following Treatment with Alemtuzumab at Month 0 and Month 12 in CAMMS323 and CAMMS324



Lymphocyte depletion and repopulation after two courses of therapy in CAMMS323 and CAMS324, with follow-up time in Extension Study CAMMS03409 shown.

Lymphocytes repopulated after depletion, with the time to reach repopulation milestones at the 12 mg dose varying by subset. By 12 months after each treatment cycle in the Phase 3 studies:

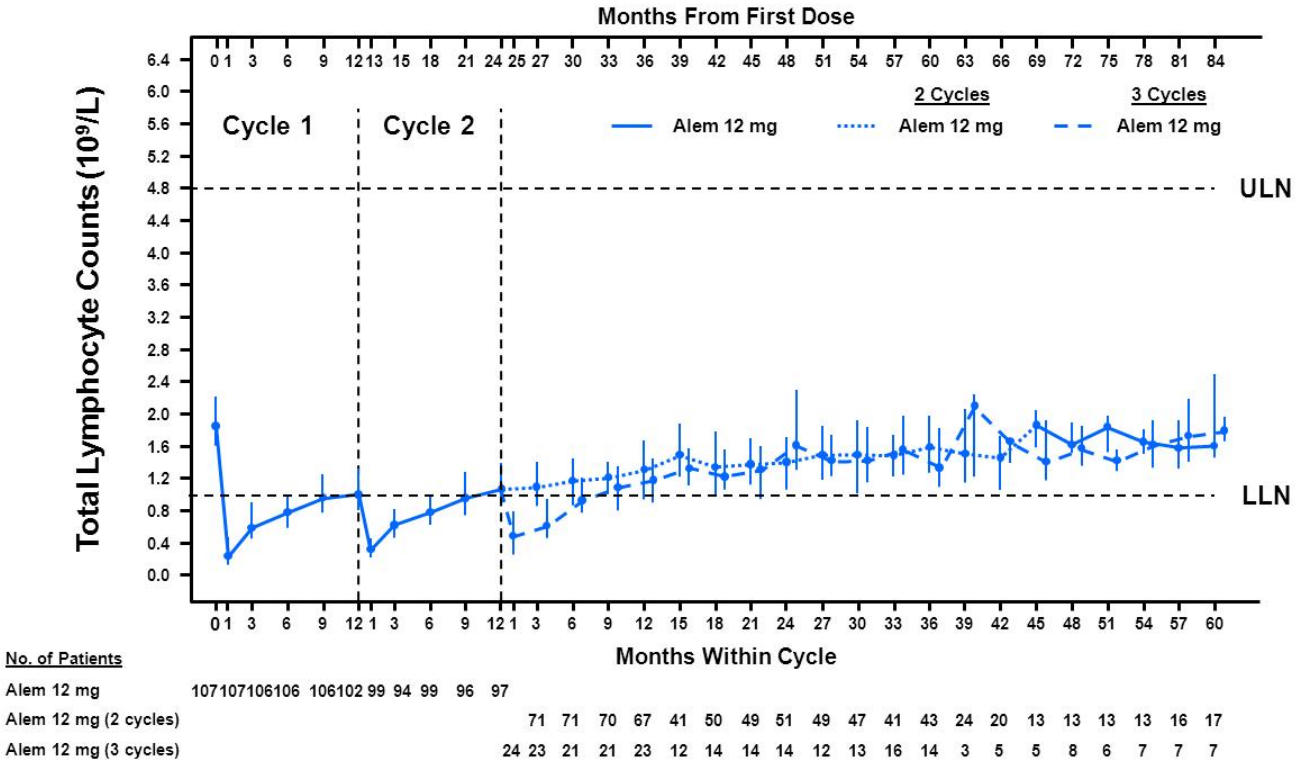
- Approximately 85% of patients had total lymphocyte counts reaching the lower limit of normal (LLN). The total lymphocyte count continued to increase during the next 24 months of follow-up (i.e., 2 years following the last visit in the Phase 3 study), but the median count remained below Baseline.
- Approximately 80% of patients had CD4+ counts ≥200 x10^6/L, and 10% had reached the LLN. The CD4+ lymphocyte count continued to increase during subsequent follow-up; the median reached the LLN around 24 months after Cycle 2, but remained below Baseline..
- Approximately 60% of patients had CD8+ counts reaching the LLN. The CD8+ lymphocyte count continued to increase during the next 24 months of follow-up, but the median count remained below Baseline.

- Approximately 99% of patients had CD19+ counts that reached LLN, and the median $CD19^+$ lymphocyte count had recovered to the Baseline value or slightly above. The $CD19^+$ lymphocyte count remained stable thereafter.
- NK cells were reduced to a lesser extent than T and B cells, with mean counts remaining within the normal range, which may relate to the greater expression of CD52 antigen on T and B lymphocytes as compared to NK cells.

A pharmacodynamic model-based evaluation was performed which suggested that lymphocyte counts did not further decrease with increasing AUC or Cmax. No effect of age, race or gender on the PD of alemtuzumab was observed.

In order to evaluate the long-term pharmacodynamic effect of alemtuzumab, lymphocyte phenotyping data from patients initially treated in the Phase 2 study CAMMS223 were analysed longitudinally from initial study entry through follow-up in the Extension study CAMMS03409 (i.e., from Baseline through 31 December 2011). Analysis showed consistent depletion of all lymphocyte subsets after alemtuzumab with lowest values observed at the earliest post-treatment time point and subsequent rise in cell count until re-exposure (Figure 27).

Figure 27: Median Total Lymphocyte Counts Over Time: CAMMS223 and CAMMS03409



Results from expanded lymphocyte phenotyping in exploratory substudies in CAMMS323 and CAMMS324 showed that among subsets of CD4+ and CD8+ T cell populations, naïve cells were depleted to a relatively greater extent than memory cells at Month 1 after alemtuzumab treatment. The percentages of both cell types returned to baseline by Month 12. The proportion of cells of regulatory T cell phenotype increased from baseline to Month 1 and then gradually returned towards baseline levels, although the percentage of cells remained elevated at Month 12. The same patterns for each phenotype were observed after the second alemtuzumab cycle.

6.1.1.3 Clinical Pharmacology Conclusions

The distinctive pattern of T and B cell repopulation following alemtuzumab treatment is intriguing and potentially relates to the product's mechanism of effect in MS patients. The primary intent of lymphocyte-directed therapy in MS patients is to reduce lymphocyte-mediated inflammation in the CNS and thereby mitigate disease. Alemtuzumab appears to accomplish this aim, and its observed pharmacodynamic effects suggest 2 possible ways by which it may act. First, there is a reduction in T and B lymphocyte counts immediately following treatment. The absolute abundance of nearly all lymphocyte subsets is reduced following alemtuzumab administration, which could contribute to the observed reduction in MS disease activity. Second, the distinctive pattern of repopulation that begins within weeks and continues over time could indicate a possible rebalancing of the immune system in ways that persist beyond the actual course of treatment.

The increased representation of T regulatory cells and other observed changes in repopulating lymphocyte subsets after alemtuzumab treatment provide an immunologically plausible alternative mechanism that could mediate the therapeutic activity of alemtuzumab in MS patients. It is also notable that despite significant effects on lymphocytes, components of the innate immune system such as neutrophils, monocytes, eosinophils, and basophils were only transiently affected by alemtuzumab treatment or not at all. This confirms the observations of Hu et al. which demonstrated in a nonclinical model that alemtuzumab acts on the adaptive immune system, with minimal or transient effects on circulating cells of the innate immune system (Hu, 2009, *Immunology*).

6.1.2 Immunogenicity

The development of antibodies to other humanized monoclonal antibodies, e.g., infliximab and natalizumab, has been associated with an increase in infusion-related adverse reactions and, for some patients, reduced efficacy (Baert, 2003, *New Engl J Med*; Stüve, 2007, *CNS Drug Reviews*; Tysabri, US Prescribing Information, 2013).

Data for alemtuzumab discussed here is derived from the Phase 3 studies which used a 3-tiered testing approach for assessment of immunogenicity in which patient samples were screened for binding antibodies, confirmed for binding specificity and any positive samples were then further evaluated for in vitro inhibition. All immunogenicity assays were validated for use in the Phase 3 studies.

Overall, a majority (691/811, 85.2%) of patients treated with 12 mg/day alemtuzumab in the pooled Phase 3 studies tested positive for anti-alemtuzumab antibodies during the course of the study (Figure 28). Of the 85.2% of patients who tested positive for anti-alemtuzumab antibodies at any time point during the course of the study, 92.2% (637/691) tested positive for inhibitory antibodies. As shown in Figure 26, and a higher proportion of patients tested positive for anti-alemtuzumab antibodies in Cycle 2 than Cycle 1. In general, the percentage of patients with antibodies peaked at 1 to 3 months after treatment and decreased thereafter until the next treatment cycle was administered. Peak antibody titers for anti-alemtuzumab were higher following Cycle 2 than Cycle 1 Figure 29. Similar trends were observed in incidence and timing of peak titers for those patients who tested positive for inhibitory antibodies.

Figure 28: Proportion of Patients with Positive Anti-Alemtuzumab Antibody Titers over Time, CAMMS323 and CAMMS324

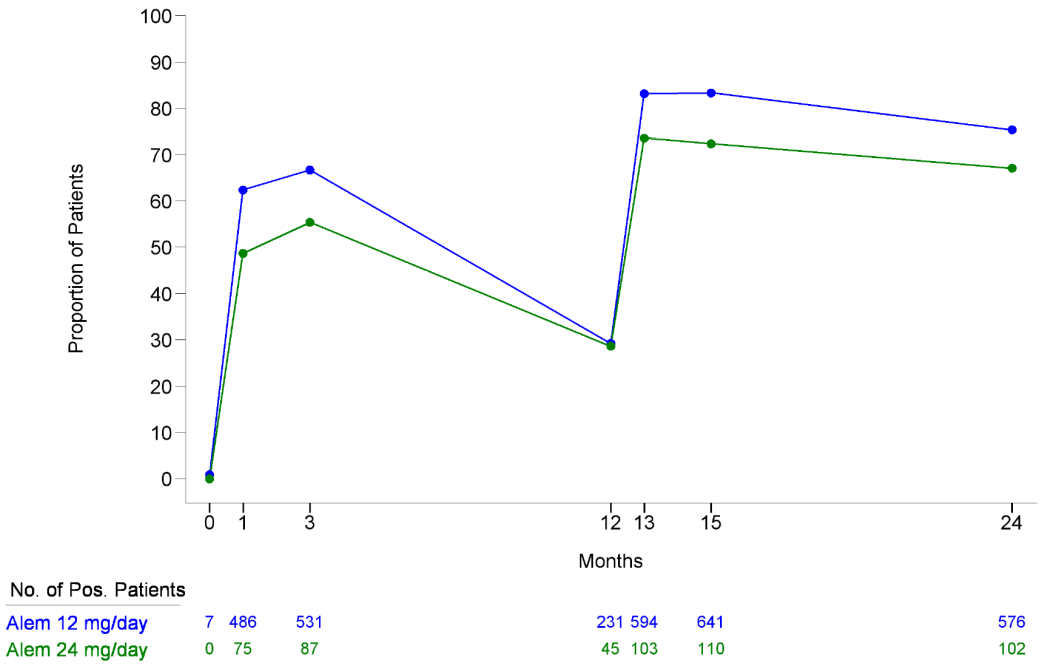
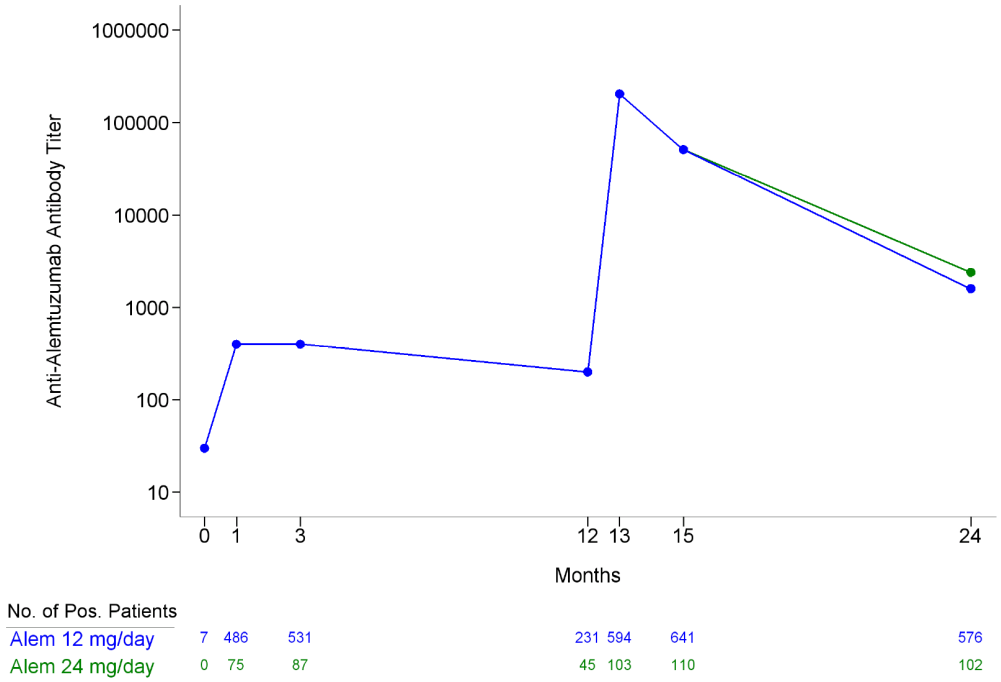


Figure 29: Median Anti-Alemtuzumab Antibody Titer over Time, CAMMS323 and CAMM324



Through 2 cycles of treatment with alemtuzumab 12 mg/day, the presence and titer level of anti-alemtuzumab or inhibitory antibody generally had no discernible effects on T or B lymphocyte depletion or repopulation. The reduction in lymphocyte count following alemtuzumab administration was not affected by anti-alemtuzumab antibody status.

In contrast to what has been observed with beta-interferon (Vartanian, 2004, *J Neurol*) and natalizumab (Stüve, 2007, *CNS Drug Rev*), the presence of these anti-alemtuzumab antibodies had no effect on clinical efficacy or safety. This may be explained by the annual dosing regimen, the low levels of circulating anti-alemtuzumab antibodies at initial treatment and just prior to retreatment(s) 12 months later, and the rapidity of lymphocyte depletion upon drug exposure. However, even though the data on 2 treatment courses may be definitive in this regard, it is unclear whether additional courses of treatment and increasing antibody titers might eventually impact alemtuzumab's pharmacological effects.

The presence or magnitude of anti-alemtuzumab antibodies and inhibitory antibodies and the incidence of adverse events (AE) and infusion associated reactions (IAR) was also evaluated. No major differences were seen in the overall incidence of IARs or AEs between patients who

were positive for anti-alemtuzumab and inhibitory antibodies and patients who were always negative, and in general this trend was also observed when patients who were ever positive were stratified by peak antibody quartiles.

Binding and inhibitory antibodies showed similar temporal trends and similar lack of influence on pharmacodynamic, efficacy, and safety outcomes.

7. Risk Mitigation Strategy

Genzyme is committed to ensuring the benefits of alemtuzumab outweigh the risks. While the established safety profile, including common adverse events and precautions will be communicated to physicians via labelling, there are important risks identified with the use of alemtuzumab that warrant additional Pharmacovigilance measures beyond that of standard labelling to better ensure patient safety. As such, Genzyme has developed a comprehensive risk management plan to educate physicians and patients regarding important risks, to monitor for key adverse events in an effort to mitigate their severity and to continue surveillance efforts to further characterize the long-term safety profile. As part of this risk mitigation strategy, a formal Risk Evaluation and Mitigation Strategy (REMS) will be implemented through which distribution of alemtuzumab will be restricted to certified prescribers.

7.1 Labelling

Specific labelling for alemtuzumab as used in MS will be adopted apart from the established labelling for Campath in the B-CLL population in an effort to clearly communicate and enhance understanding of the recommended dose, observed safety profile, and appropriate conditions for use of alemtuzumab in MS. This is not an unprecedented occurrence as there are multiple examples of a single drug product with separate labelling based on indication (e.g., denosumab).

Important differences in the safety profile have been established that require specific warnings and precautions for the MS population such as the common occurrence of thyroid disorders which must be monitored over a prolonged period of time. Most notably, the observation of such autoimmune mediated adverse events within the MS clinical trials identified a risk somewhat unique to the MS population that necessitates prominence in labelling, especially in light of the required monitoring for such events for several years after exposure to alemtuzumab. For example, in contrast to the observed events in MS patients, ITP is part of the natural history of progressive CLL. Therefore, it is known by oncologists that patients with B-CLL have a risk for the development of cytopenias such as ITP given their underlying disease (background incidence

of ITP of roughly 2% in patients with hematological malignancies; Cheson, B.D., 2001. *Cancer: Principles and Practice of Oncology*.; Diehl, 1998, *Semin Oncol*). Since ITP would not be a frequent event in the natural history of MS, a neurologist prescribing alemtuzumab for a patient with MS must have clear instruction as to the incidence and potential severity of ITP, the premonitory signs and symptoms, and the recommended monitoring to detect such an event in an effort to avoid significant morbidity.

Accordingly, the labelling for alemtuzumab in MS will include a boxed warning relative to the occurrence of autoimmune AEs such as ITP and anti-GBM disease and note the required monitoring to detect such events. Given the potential for serious outcomes if such autoimmune AEs are not promptly identified and treated, the boxed warning will also note that alemtuzumab as used in MS will only be available via a restricted distribution program so that physicians prescribing the drug and patients receiving therapy are enrolled in the program and appropriately trained on and/or advised of these serious risks prior to use of the drug.

While separately labelling is proposed in MS, safety experience with Campath provides important information to help characterize the potential for common events to occur at a greater severity or with a more serious nature when given at higher and more frequent doses. As such, information relative to serious IARs, infections and cytopenias observed with Campath has been incorporated into the Warnings/Precautions and Adverse Event sections of the labelling for alemtuzumab in MS.

Patient education and symptom monitoring was an integral part of risk management activities in the clinical program and proved a valuable tool in early identification of autoimmune AEs. The patient is the key stakeholder in any decision relative to risk and in the setting of a chronic disease often become a self-advocate with great awareness of their medical history and health status. As such, patient directed labelling is an important element of informing a patient relative to risks and the conditions for safe use of any therapy. Since prompt identification and treatment are an important component of mitigating serious outcomes associated with autoimmune adverse events related to treatment with alemtuzumab, a Medication Guide has been proposed in order to appropriately inform patients relative to these risks. The Medication Guide provides written details/graphic representations of potential symptoms of autoimmune disorders, including ITP, nephropathy and thyroid disease. Further, it provides information on the urgency with which a patient should contact a medical professional should they observe such symptoms. The labelling also conveys the critical need to undergo required lab monitoring as a condition of use of alemtuzumab.

7.2 REMS

Genzyme believes that the benefit-risk profile of alemtuzumab can be better assured through the implementation of a Risk Evaluation and Mitigation Strategy (REMS) that includes restricted distribution (an element to assure safe use under the regulatory framework for REMS). Accordingly, a REMS program for alemtuzumab in MS has been designed in consideration of the following goals:

- To educate patients and health care providers (HCPs) about the serious risks associated with the use of Lemtrada, including autoimmune conditions (immune thrombocytopenic purpura [ITP], thyroid disorders, and nephropathies) and serious infections.
- To mitigate the severity and sequelae of incident autoimmune events (ITP, thyroid disorders, and nephropathies [including anti-GBM disease]) and serious infections by through monitoring and prompt identification of signs and symptoms of these events.

A review of the integrated safety database for alemtuzumab, with particular focus on the onset and method of identification of autoimmune mediated events indicates that the monitoring elements piloted in the clinical program were effective in identifying such AEs. In particular, in assessing the time of onset of ITP, nephropathies and thyroid disorders from the most recent dose of alemtuzumab, all but one event had occurred within 48 months of last exposure (Figure 24). This suggests that monitoring of patients for 48 months following the last dose of alemtuzumab is appropriate for identification and treatment of potential autoimmune events. As such, required lab testing under the risk management program is outlined in Table 42.

Table 42: Laboratory Monitoring for Patients Receiving Alemtuzumab

Lab Measurement	Risk	Timing
CBC with differential	ITP	Prior to treatment and monthly for 48 months after last infusion
Thyroid function tests, such as TSH level	Thyroid disorders	Prior to treatment and quarterly for 48 months after last infusion
Serum creatinine	Nephropathies	Prior to treatment and monthly for 48 months after last infusion

Table 42: Laboratory Monitoring for Patients Receiving Alemtuzumab

Lab Measurement	Risk	Timing
Urinalysis with urine cell counts	Nephropathies	Prior to treatment and quarterly for 48 months after last infusion

Because adherence to these monitoring requirements is necessary in order to promptly detect and treat incident autoimmune AEs, Genzyme proposes to implement a restricted distribution model that will limit access to alemtuzumab to those physicians and infusion clinics educated and trained regarding these risks and requirements. Elements of the restricted distribution program under the REMS include, but are not limited to:

- Physician
  - Complete company-sponsored training in order to become certified;
  - Documented certification required in order to prescribe alemtuzumab;
  - Acknowledge understanding of and willingness to comply with all program requirements;
  - Enroll each patient to be treated with alemtuzumab in the REMS program;
  - Counsel each patient on the risks associated with use of alemtuzumab and the need to comply with lab monitoring;
  - Provide each patient with a copy of the Medication Guide;
  - Monitor every patient in accordance with labelled lab test requirements;
  - Agree to participate in surveys to assess understanding of educational materials and risk information;
  - Acknowledge that a failure to comply with program requirements may result in the loss of certification and an inability to prescribe alemtuzumab.
- Infusion Clinic
  - Complete company sponsored training in order to become certified;

- Documented certification required in order to dispense alemtuzumab;
- Acknowledge understanding of and agree to develop institutional procedures to comply with all program requirements;
- Verify and document physician and patient enrolment in the REMS program prior to dispensing alemtuzumab;
- Provide each patient with a copy of the patient labelling on the first day of each infusion course;
- Undergo audit as necessary to assure compliance with program requirements; and
- Acknowledge that a failure to comply with program requirements may result in the loss of certification and an inability to dispense alemtuzumab.

- Genzyme (REMS program hub)
  - Provide training for all program participants;
  - Re-train all program participants should program requirements change;
  - Verify enrolment of physician and healthcare facility before authorizing shipment of drug;
  - Institute policies to address non-compliance;
  - Audit a proportion of program participants annually to monitor compliance;
  - Maintain a secure and validated database of all program participants, including certification status; and
  - Provide support services for patients such as central lab services, nursing support and periodic reminders for testing.

In addition, the patient will have an integral role in the risk mitigation process through their awareness of and vigilance in monitoring for the development of symptoms of autoimmune disorders and serious infections. Patients will be educated via the Medication Guide and required counselling by their physician on the need to comply with lab testing for 4 years following last administration of alemtuzumab and to immediately report symptoms of potentially serious adverse events. Under the REMS, patients will be required to:

- Be enrolled in the program by their physician;
- Read the Medication Guide provided by their physician and the infusion clinic at the time of infusion;
- Confirm counselling was provided by their physician on the risks associated with alemtuzumab;
- Confirm understanding of long-term monitoring requirements;
- Agree to undergo the required monthly lab tests;
- Know the signs/symptoms of autoimmune disorders and serious infections;
- Immediately report these symptoms to their physician; and
- Opt in for lab test reminders and support services as appropriate.

While the monitoring and program enrollment requirements are rigorous, they will not be novel among the landscape of MS therapies as other drugs currently prescribed in the US are available only under a REMS program. In particular, physicians in the US are familiar with restricted distribution requirements in place since 2007 for natalizumab.

7.3 Post Marketing Safety Surveillance

As part of Genzyme's commitment to further evaluate the safety profile of alemtuzumab in MS, a post-authorization safety study (PASS) was proposed as a formal commitment to FDA (mandatory post-marketing requirement). The PASS intends to collect information through a prospective, multicenter, observational cohort of patients with relapsing forms of multiple sclerosis followed for 5 years regardless of duration of treatment. The primary objective is to determine the incidence rates of safety events of interest in patients who receive alemtuzumab, specifically serious infection, malignancy, and auto-immune mediated conditions including ITP, cytopenias, thyroid disorders, and nephropathies.

In order to more accurately describe the incidence of such AEs and to be able to detect events with expected incidence of 0.2% over a 5-year follow-up period, it is planned to recruit a total of 5,000 first-time initiators of treatment with alemtuzumab from global study sites. To fully characterize risks, incidence rates observed in this study will be compared with rates observed in an external comparison group of patients with MS who have not been exposed to alemtuzumab

to determine how the risk of adverse events in RMS patients exposed to alemtuzumab compares with rates of the same events observed in MS who are not treated with alemtuzumab.

In addition, as there are limited data on pregnancy from the clinical studies of alemtuzumab (Section 5.1.8.5), Genzyme has proposed to conduct a prospective, observational pregnancy registry in order to assess pregnancy outcomes in women exposed to alemtuzumab during pregnancy.

7.4 Summary of Risk Management Activities

Through these efforts to educate all key stakeholders through labelling and other materials, to restrict distribution to certified prescribers and infusion clinics and to continue to further characterize the safety of alemtuzumab in MS through an ongoing postmarketing study, Genzyme believe the benefit/risk of treatment with alemtuzumab will be better assured for patients with MS.

8. Benefit Risk Considerations

As a leading cause of neurological disability in young adults, MS is a serious disease with significant long-term impact. There remains a high unmet medical need in the treatment of patients with relapsing forms of MS, in terms of therapies to more effectively suppress relapses, and thus prevent (or reduce) the accumulation of disability. This is especially relevant in the treatment of patients whose disease course suggests severe MS and/or who have continued to experienced disease activity while on treatment.

It has become clear that treatment of early disease activity is critical as such activity is associated with long-term accumulation of irreversible disability. This view is supported by several studies demonstrating a relationship among early lesion load on MRI, relapse activity, and subsequent development of permanent disability (Weinshenker, 1989, *Brain*; Confavreux, 2003, *Brain*; Brex, 2002, *N Engl J Med*). The correlations become even stronger with extended follow-up times, or when early disease activity is determined with MRI and/or clinical measures in combination (Sormani, 2011, *Neurology*; Rudick, 2006, *Ann Neurol*; Bermel, 2013, *Ann Neurol*). Therefore, early and highly effective intervention to suppress disease activity in patients with relapsing forms of MS may represent the best overall treatment approach for many patients.

8.1 Summary of Benefits

Two courses of alemtuzumab treatment robustly reduces the rate of relapse and accumulation of disability in patients with MS compared to high dose, high frequency Rebif. The treatment effects become apparent within a few months of the first treatment course, and low rates of

relapse and SAD are sustained through at least 3 years of follow up, without most patients receiving additional courses of treatment. The results presented here support the use of alemtuzumab in a broad range of patients with relapsing forms of MS, encompassing treatment-naïve patients with active disease as well as patients who have experienced continued clinical disease activity while on prior therapy.

Efficacy data from the randomized, rater-blinded studies showed that alemtuzumab was more effective on relapse rates than Rebif, both in treatment-naïve patients with active disease (studies CAMMS323 and CAMMS223), as well as in patients with an inadequate response to prior therapy (CAMMS324).

Time to 6-month SAD assessment revealed superior effects of alemtuzumab on this endpoint in Phase 3 study CAMMS324 and this result was supported by results of the Phase 2 study CAMMS223. While a statistically significant treatment effect was not observed for time to 6-month SAD in Phase 3 Study CAMMS323, the estimated 30% treatment effect is also supportive of a disability effect with alemtuzumab.

Uniquely, alemtuzumab-treated patients in CAMMS324 and CAMMS223 experienced an improvement in their level of physical disability while the Rebif group experienced a net worsening. Significant improvement with alemtuzumab treatment was observed in the mean change from baseline as well as the proportion of patients experiencing a sustained reduction in disability score. This latter analysis, performed in patients with pre-existing disability (minimum EDSS of 2.0), demonstrated that a substantial number of patients (29% in CAMMS324) experienced improvements in disability of sufficient magnitude (≥ 1 EDSS point) and persistence (sustained for ≥ 6 months) to be clinically meaningful. None of the approved DMTs has shown a similarly increased likelihood of disability improvement in an active comparator trial.

Effects on clinical endpoints were mirrored and supported by significant effects on a range of imaging endpoints that reflect acute disease activity (e.g., gadolinium-enhancing lesions) as well as disease progression (e.g., T2-hyperintense & T1-hypointense lesions). Further, these effects were established against a comparator (Rebif) with documented substantial effects on imaging parameters. Alemtuzumab also demonstrated a strong reduction in the rate of brain volume loss as determined by BPF, a measure of brain atrophy associated with disability progression (Gauthier, 2007, *Neurology*) and cognitive impairment (Deloire, 2011, *Neurology*).

The magnitude of alemtuzumab's treatment effects on diverse efficacy measures as compared with Rebif was large in both relative and absolute terms, and highly clinically relevant. Rebif is

an approved therapy for patients with relapsing forms of MS and, until now, no DMT for MS has been shown in a head-to-head study to be more effective than any high dose, high frequency Rebif. Alemtuzumab represents an improvement over a current standard of care in reducing the frequency of clinical exacerbations and, importantly, in slowing and reducing the accumulation of physical disability.

Alemtuzumab is administered by IV infusion in a unique dosing regimen of two annual treatment courses (12 mg/day for 5 days followed 12 months later by a further 3 days of treatment). As treatment noncompliance is regrettably common with other injectable DMTs such as interferons and glatiramer acetate (Steinberg, 2010, *Clin Drug Investig*; Devonshire, 2011, *Eur J Neurol*; Tan, 2011, *Adv Ther*; Wong, 2011, *Can J Neurol Sci*), alemtuzumab dosing may offer additional benefit through improved treatment compliance.

8.2 Summary of Risks

The risks associated with alemtuzumab treatment during the clinical program were identifiable and generally manageable. No clinically meaningful differences were observed in the safety profile of alemtuzumab between treatment-naïve patients and those with an inadequate response to prior therapy. Clinical trials with alemtuzumab in MS patients have shown a consistent safety profile, with risks that include IARs, infections and autoimmune disorders (thyroid disorders, ITP and nephropathies such as anti-GBM disease). Measures to detect and manage these effects were implemented early and refined throughout the clinical program. Once implemented, these measures enabled the management of patients within the studies and have laid a foundation for the care of patients outside of the clinical trial setting.

Nearly all alemtuzumab-treated patients experienced IARs, but these events were most often mild or moderate in severity and generally did not prevent patients from completing scheduled alemtuzumab treatment cycles and remaining in the studies. One case of anaphylaxis was reported, but there were no events of severe cutaneous reactions, such as Stevens-Johnson syndrome. Prophylactic treatment with corticosteroids was useful in preventing some IARs and is included in the proposed label for alemtuzumab in MS patients.

Both alemtuzumab and Rebif treatment groups had a high rate of infections in the clinical studies, although alemtuzumab was associated with a higher risk. However, there was no increase in the incidence or rate over time that would indicate cumulative immunosuppressive effects of continued treatment. Infections were usually mild or moderate in severity, and responded to conventional management measures. Prophylactic acyclovir treatment was used

effectively in the clinical studies to reduce risk of HSV at the time of infusion. Despite significant depletion of lymphocytes following alemtuzumab treatment, there was no predictive relationship between lymphocyte counts and the subsequent occurrence of infection AEs in alemtuzumab-treated patients. The repopulation kinetics of white blood cell subsets following alemtuzumab treatment, the lack of additive effects on white blood cell depletion with additional treatment cycles, preservation of innate immunity and relative sparing of memory lymphocytes, together with the preservation of serum immunoglobulins (Coles, 1999, *Lancet*), may contribute to the relatively low rate of serious infections and lack of cumulative risk following alemtuzumab treatment in MS patients.

Alemtuzumab treatment may increase the risk of autoimmune-mediated conditions. Observed autoimmune thyroid disorders included both hyperthyroidism and hypothyroidism, which occurred at similar rates. No consistent pattern was observed with regards to time of onset after treatment initiation, although the highest incidence of thyroid AEs was observed between 24 and 42 months after the first treatment cycle, indicating some element of latency. Therefore, as part of the risk minimization strategy for autoimmune disorders, it is proposed that thyroid function tests be obtained prior to the initiation of alemtuzumab treatment and every 3 months thereafter until 48 months following the last infusion. This will allow the early detection and treatment of thyroid disorders for patients treated with alemtuzumab.

ITP and nephropathies (including anti-GBM disease), although potentially more serious than thyroid disorders, were observed infrequently. The fatality in the index case of ITP highlights the seriousness of the risks associated this and related disorders. However, risk minimization measures (including monthly CBCs) introduced to monitor for ITP and other potential autoimmune cytopenias in the clinical studies allowed the prompt diagnosis and treatment of patients who subsequently developed the condition and will serve as the foundation for planned post-marketing risk minimization efforts. Despite the rarity of anti-GBM disease in the clinical program, the monthly frequency of serum creatinine testing was effective in identifying cases early to allow prompt treatment and is considered an appropriate monitoring tool by nephrologists. Similarly, urinalysis testing was also effective in identifying a number of nephropathies during the clinical studies. As for thyroid disorders, monitoring for ITP and nephropathies is proposed from the initiation of treatment through to 48 months after last alemtuzumab infusion. This seems appropriate based on the observations and long-term follow-up data available from the clinical studies. No clinically useful predictor of risk has yet been identified for autoimmune disorders. In the absence of such information, the data from the risk

minimization activities, particularly from Phase 3, are informative regarding the ability of such measures to detect events in a timely manner to help mitigate severity and sequelae of incident autoimmune disorders.

During the course of the clinical studies, malignancies were observed in both alemtuzumab-and Rebif-treated patients. However, the annualized rates of malignancy were similar across all treatment groups, and moreover, the malignancy risk was similar to the background incidence in the general population.

Although treatment with alemtuzumab was observed to result in the formation of anti alemtuzumab antibodies in the majority of patients, these were not associated with IARs. In fact, the data indicate no detrimental effect of such antibody formation on the efficacy, safety, or pharmacodynamics of alemtuzumab.

The recommended dosing regimen for alemtuzumab consists of 2 annual treatment courses of 12 mg/day (12 mg/day for 5 days followed 12 months later by a further 3 days of treatment). Physicians in the clinical studies were permitted to administer additional courses of treatment after the two initial treatment courses in the setting of MS disease activity. Approximately 20% of patients received additional treatment courses (12 mg/day for 3 days) and approximately 3% received additional MS treatments. It is anticipated that a similar approach to additional courses of treatment will be taken in the commercial setting. Additional alemtuzumab treatment courses were not associated with any meaningful increases in frequencies of clinically important adverse events and there was no evidence that additional retreatment lead to cumulative toxicity.

A 24 mg/day dose of alemtuzumab was also studied in the Phase 2 CAMMS223 study and, in an exploratory fashion, in the Phase 3 CAMMS324 study. There were no notable differences between the alemtuzumab 12 mg/day and 24 mg/day groups with regards to the preferred terms of common IARs reported. However, the incidences of IARs were generally higher in the alemtuzumab 24 mg/day group with a higher incidence also of severe (Grade 3 and 4) IARs, suggesting improved tolerability of the 12 mg/day dose. Further, it was noted that while the 12 mg/day and 24 mg/day doses appeared to have similar efficacy on most clinical endpoints, there was some reduction in efficacy on imaging endpoints with the 12 mg/day regimen, suggesting that further reductions in dose would likely lead to further reductions in efficacy. Therefore, the 12 mg/day dose appears to be optimal from a benefit-risk standpoint and is thus the proposed dose for licensing.

8.3 Conclusions

Alemtuzumab modulates the immune system through lymphocyte depletion and repopulation, and effectively suppresses inflammatory autoimmune processes that lead to MS relapse and disability progression. All currently approved DMTs for MS have been shown to be effective at reducing relapses and, in some cases, slowing disability accumulation; however, none have been shown to be more effective on critical clinical and imaging endpoints than a high frequency, high dose interferon such as Rebif. The clinical development program for alemtuzumab is the first program in MS patients to be designed with an active comparator control (Rebif) in all of the controlled clinical studies of efficacy and safety. Alemtuzumab has been shown to be superior to Rebif on important clinically-based relapse and disability endpoints, as well as multiple brain imaging endpoints. In addition to slowing or delaying disability progression, alemtuzumab treatment increased the likelihood of improvement in pre-existing disability (as indicated by improved scores on multiple domains of the EDSS in studies CAMMS223 and CAMMS324).

Based on the clinical safety experience with alemtuzumab including 1,486 patients with MS treated with alemtuzumab and >5,400 patient-years of collective follow-up, a robust risk minimization program has been developed and implemented. Restricted distribution of alemtuzumab under the proposed REMS will further ensure that only prescribers and patients who fully understand the risks of treatment and who agree to the safety monitoring program will be granted access to alemtuzumab.

Importantly, alemtuzumab was shown to be highly efficacious both in patients who are naïve to treatment and in patients who had an inadequate response to prior therapies and for whom limited treatment options exist. Additionally, the infrequent treatment courses for alemtuzumab provide a very different experience compared with all other DMTs, and may be preferable for many patients who are currently required to take their MS medication continuously on a schedule ranging, for different products, from twice daily to monthly. With a unique mechanism of action and a compelling efficacy profile established versus a high frequency, high dose interferon, alemtuzumab represents a highly efficacious and important addition to the armamentarium of therapies at the disposal of neurologists treating patients with MS.

9. References

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10. Appendices

10.1 Appendix A

Disease Modifying Therapies Approved for MS

DMT / Approval Date	Effect on Relapse: % relapse free at 2 years	Effect on Disability: % with sustained progression	Effect on disability vs. active comparator	Key Warnings/Safety Information
Betaseron® (interferon beta-1b) /1993	25% Betaseron 16% placebo	None labeled	No	Hepatic injury; anaphylaxis/ other allergic reactions; depression and suicide; congestive heart failure; injection site necrosis/ reactions; leukopenia; flu-like symptom complex, seizures.
Avonex® (interferon beta-1a) /1996	38% Avonex 26% placebo	sustained for 6 months: 22% Avonex 35% placebo	No	Depression, suicide, and psychotic disorders; hepatic injury; anaphylaxis/other allergic reactions; congestive heart failure; decreased peripheral blood counts; autoimmune disorders
Rebif® (interferon beta-1a) /2002	32% Rebif 15% placebo	sustained for 3 months: 26% Rebif 39% placebo	No	Depression and suicide; hepatic injury; anaphylaxis
Extavia® (interferon beta-1b) /2009	25% Extavia 16% placebo	None labeled	No	Depression and suicide; injection site necrosis/ reactions; anaphylaxis; flu-like symptom complex; leukopenia; hepatic enzyme elevations
Copaxone® (glatimer acetate) /1996	34% Copaxone 27% placebo	None labeled	No	Immediate post-injection reaction; Chest pain; lipoatrophy and skin necrosis; potential to modify immune response
Tysabri® (natalizumb) /2004	67% Tysabri 41% placebo	sustained for 3 months: 17% Tysabri 29% placebo	No	Progressive multifocal leukoencephalopathy; hypersensitivity reactions; immunosuppression/ infections; hepatotoxicity
Gilenya® (fingolimod) /2010	70% Gilenya 46% placebo	sustained for 3 months: 18% Gilenya 24% placebo	No	Bradyarythmia and atrioventricular block after 1st dose; infections; macular edema; respiratory effects; hepatic effects (liver transaminases); hypertension, potential fetal risk

Disease Modifying Therapies Approved for MS

DMT / Approval Date	Effect on Relapse: % relapse free at 2 years	Effect on Disability: % with sustained progression	Effect on disability vs. active comparator	Key Warnings/Safety Information
Aubagio® (teriflunomide) /2012	57% Aubagio 46% placebo	sustained for 3 months: 20% Aubagio 27% placebo	No	Hepatotoxicity; use in pregnancy; infection; peripheral neuropathy; acute renal failure; severe skin reaction; hyperkalemia, blood pressure increase
Tecfidera® (dimethyl fumarate) /2013	73% Tecfidera 54% placebo	sustained for 3 months: 16% Tecfidera 27% placebo	No	Lymphopenia, flushing, gastrointestinal effects, increased hepatic transaminases, eosinophilia

Note: Information derived from current US Prescribing Information.

10.2 Appendix B

Inclusion and Exclusion Criteria for Study CAMMS223

Inclusion Criteria

1. Signed ICF.
2. Male or non-pregnant, non-lactating female patients, 18 to 50 years of age (inclusive) as of signing the ICF.
3. Diagnosis of MS per McDonald's update of the Poser criteria, including cranial MRI consistent with those criteria (McDonald, 2001, Ann Neurol).
4. Onset of first MS symptoms within 3 years prior to screening as of signing the ICF.
5. EDSS score 0.0 to 3.0 (inclusive) at the screening and baseline visits.
6. At least 2 completed clinical episodes of MS in the 2 years prior to study entry (i.e., the initial event if within 2 years of study entry plus at least 1 relapse, or at least 2 relapses if the initial event was between 2 and 3 years prior to study entry).
7. In addition to the clinical criteria (i.e., Items 3 to 6 above), at least 1 enhancing lesion on any 1 of up to 4 screening gadolinium-enhanced MRI brain scans during a maximum 3-month run-in period (inclusive of the Month 0 baseline scan).

Exclusion Criteria

Patients fulfilling any of the following criteria were excluded from study participation:

1. Previous immunotherapy for MS other than steroids, including treatment with interferons, intravenous immunoglobulin (IVIG), glatiramer acetate, and mitoxantrone.
2. Personal history of thyroid autoimmune disease.
3. Personal history of clinically significant autoimmune disease (e.g., inflammatory bowel disease, diabetes, lupus, severe asthma).
4. History of thyroid carcinoma (previous thyroid adenoma was acceptable and was not considered an exclusion criterion).
5. History of malignancy (except for basal cell skin carcinoma if disease-free for at least 5 years).
6. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, interfered with evaluation of disability due to MS.
7. Previous treatment with alemtuzumab.
8. History of anaphylaxis following exposure to humanized monoclonal antibodies.

9. Inability to undergo MRI with gadolinium administration.
10. Female patients of childbearing potential with a positive serum pregnancy test at screening or baseline.
11. Males and females who did not agree to use effective contraceptive method(s) during the study.
12. Impaired renal function (serum creatinine ≥2 times upper limit of normal [ULN]).
13. Untreated, major depressive disorder.
14. Epileptic seizures that were not adequately controlled by treatment.
15. Suicidal ideation.
16. Major systemic disease or other illness that would, in the opinion of the Investigator, have compromised patient safety or interfered with the interpretation of study results.
17. Abnormal CD4 count or significantly abnormal thyroid function; presence of anti-thyroid stimulating hormone (TSH) receptor antibodies; known seropositivity for human immunodeficiency (HIV).
18. Intolerance of pulsed corticosteroids, especially a history of steroid psychosis.
19. Presence of a monoclonal paraprotein.
20. Patients who had any form of MS other than relapsing-remitting.
21. Patients currently participating in a clinical study of an experimental or unapproved/unlicensed therapy.

Inclusion and Exclusion Criteria for Study CAMMS323

Inclusion Criteria

1. Given written/signed informed consent
2. Age 18 to 50 years old (inclusive) as of the date the ICF was signed
3. Diagnosis of MS per updated McDonald criteria, and cranial MRI scan demonstrating white matter lesions attributable to MS within 5 years of screening
4. Onset of MS symptoms (as determined by a neurologist, either at screening or retrospectively) within 5 years of the date the ICF was signed
5. EDSS score 0.0 to 3.0 (inclusive) at screening
6. ≥ 2 MS attacks (first episode or relapse) occurring in the 24 months prior to the date the ICF was signed, with ≥ 1 attack in the 12 months prior to the date the ICF was signed,

with objective neurological signs confirmed by a physician, nurse practitioner, or other Genzyme-approved health-care provider. The objective signs could be identified retrospectively.

Exclusion Criteria

1. Current participation in another clinical study
2. Received prior therapy for MS other than corticosteroids, e.g., alemtuzumab, interferons, IV immunoglobulin, glatiramer acetate, natalizumab, and mitoxantrone
3. Exposure to azathioprine, cladribine, cyclophosphamide, cyclosporine A, methotrexate, or any other immunosuppressive agent other than systemic corticosteroid treatment
4. Received treatment with a monoclonal antibody for any reason
5. Previous treatment with any investigational medication, i.e., a drug not approved at any dose or for any indication (Prior treatment with herbal medications or nutritional supplements was permitted)
6. Any progressive form of MS
7. History of malignancy (except basal skin cell carcinoma)
8. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS
9. Previous hypersensitivity reaction to any immunoglobulin product
10. Known allergy or intolerance to interferon beta, human albumin, or mannitol
11. Intolerance of pulsed corticosteroids, especially a history of steroid psychosis
12. Inability to self-administer SC injections or receive SC injections from caregiver
13. Inability to undergo MRI with gadolinium administration
14. CD4+ cell count (absolute CD3+CD4+) < lower limit of normal (LLN) at screening
15. CD8+ cell count (absolute CD3+CD8+) <LLN at screening
16. B-cell count (absolute CD19+) <LLN at screening
17. Absolute neutrophil count <LLN at screening
18. Known bleeding disorder (e.g., dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, disseminated intravascular coagulation, fibrinogen deficiency, or clotting factor deficiency)
19. Seropositivity for human immunodeficiency virus (HIV)

20. Significant autoimmune disease including but not limited to immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis
21. Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (i.e., above the LLN)
22. Active infection, e.g., deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation
23. In the Investigator's opinion, at high risk for infection (e.g., indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent urinary tract infection)
24. Latent tuberculosis unless effective anti-tuberculosis therapy course was completed, or active tuberculosis.
25. Infection with hepatitis C virus
26. Past or present hepatitis B infection (positive hepatitis B serology)
27. Of childbearing potential with a positive serum pregnancy test, pregnant, or lactating
28. Unwilling to agree to use a reliable and acceptable contraceptive method throughout the study period (fertile patients only). Reliable and effective contraceptive method(s) include: intrauterine device, hormonal-based contraception, surgical sterilization, abstinence, or double-barrier contraception (condom and occlusive cap [diaphragm or cervical cap with spermicide]).
29. Major psychiatric disorder not adequately controlled by treatment
30. Epileptic seizures not adequately controlled by treatment
31. Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results, e.g., current peptic ulcer disease or other conditions that could predispose to hemorrhage
32. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromised the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study
33. Confirmed platelet count < LLN of the evaluating laboratory at screening or documented at <100,000/μL within the past year on a sample without platelet clumping
34. Prior history of invasive fungal infections
35. Cervical high risk human papillomavirus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS)
36. Seropositive for Trypanosoma cruzi or the Human T-lymphotropic virus type I or type II (HTLV I/II) (testing required in endemic regions only).

37. Any other illness or infection (latent or active) that, in the Investigator's opinion, could have been exacerbated by either study medication
38. Any hepatic or renal function value Grade 2 or higher at Screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome; see Table below, drawn from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE), published 09 Aug 2006.

Inclusion and Exclusion Criteria for Study CAMMS324

Inclusion Criteria

1. Signed ICF
2. Age 18 to 55 years (inclusive) as of the date the ICF was signed
3. Diagnosis of MS per update of McDonald criteria
4. Onset of MS symptoms (as determined by a neurologist; could be retrospectively) within 10 years of the date the ICF was signed
5. An EDSS score 0.0 to 5.0 (inclusive) at Screening
6. ≥2 MS attacks (first episode or relapse) occurring in the 24 months prior to the date the ICF was signed, with ≥1 attack in the 12 months prior to the date the ICF was signed, with objective neurological signs confirmed by a physician, nurse practitioner, or other Genzyme-approved health-care provider. The objective signs could be identified retrospectively.
7. ≥1 MS relapse during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for ≥ 6 months within 10 years of the date the ICF was signed
8. MRI scan demonstrating white matter lesions attributable to MS and meeting at least 1 of the following criteria, as determined by the neurologist or a radiologist
   - ≥ 9 T2 lesions at least 3 mm in any axis
   - A gadolinium- (Gd-)enhancing lesion at least 3 mm in any axis plus ≥1 brain T2 lesions
   - A spinal cord lesion consistent with MS plus ≥1 brain T2 lesion

Exclusion Criteria

1. Previous treatment with alemtuzumab
2. Were participating in another clinical study or previously participating in CAMMS323

3. Had treatment with natalizumab, methotrexate, azathioprine, or cyclosporine in the past 6 months. Patients who received one of these medications more than 6 months before the date the ICF was signed were eligible for study entry if approval was granted by Genzyme.
4. Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab or any other immunosuppressant or cytotoxic therapy (other than steroids)
5. Previous treatment with any investigational medication (drug has not been approved at any dose or for any indication) unless prior approval granted by Genzyme and the patient completed any required washout. Use of an investigational medication that was subsequently licensed and nonstandard use of a licensed medication (e.g., using a dose other than the dose that was stated in the licensed product labelling or using a licensed therapy for an alternative indication) was not exclusionary. Prior treatment with herbal medications or nutritional supplements was also permitted.
6. Any progressive form of MS
7. History of malignancy, except basal skin cell carcinoma
8. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS
9. Previous hypersensitivity reaction to any immunoglobulin product
10. Known allergy or intolerance to interferon beta, human albumin, or mannitol
11. Intolerance of pulsed corticosteroids, especially a history of steroid psychosis
12. Inability to self-administer SC injections or receive SC injections from caregiver
13. Inability to undergo MRI with Gd administration
14. Confirmed platelet count < the lower limit of normal (LLN) of the evaluating laboratory at Screening or documented at <100,000/μL within the past year on a sample without platelet clumping
15. CD4+, CD8+, or CD19+ (i.e., absolute CD3+CD4+, CD3+CD8+, or CD19+/mm3) count <LLN at Screening; if abnormal cell count(s) returned to within normal limits (WNL), eligibility could be reassessed
16. Absolute neutrophil count <LLN at Screening; if abnormal cell count returned to WNL, eligibility could be reassessed
17. Known bleeding disorder (e.g., dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, disseminated intravascular coagulation [DIC], fibrinogen deficiency, clotting factor deficiency)
18. Seropositivity for human immunodeficiency virus (HIV)

19. Significant autoimmune disease including but not limited to: immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis
20. Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (i.e., above LLN)
21. Active infection, e.g., deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation
22. In the Investigator's opinion, at high risk for infection (e.g., indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent urinary tract infection [UTI])
23. Latent tuberculosis unless effective anti-tuberculosis therapy has been completed, or active tuberculosis
24. Infection with hepatitis C virus
25. Past or present hepatitis B infection (positive hepatitis B serology)
26. Of childbearing potential with a positive serum pregnancy test, pregnant, or lactating
27. Unwilling to agree to use a reliable and acceptable contraceptive method throughout the study period (female patients only). Reliable and effective contraceptive method(s) included: intrauterine device (IUD), hormonal-based contraception, surgical sterilization, abstinence, or double-barrier contraception (condom and occlusive cap [diaphragm or cervical cap with spermicide]).
28. Major psychiatric disorder that was not adequately controlled by treatment
29. Epileptic seizures that were not adequately controlled by treatment
30. Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results (e.g., current peptic ulcer disease, or other conditions that may have predisposes to hemorrhage)
31. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromised the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study
32. Prior history of invasive fungal infections
33. Cervical high risk human papilloma virus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS). The patient may have been eligible after the condition resolved (e.g., follow-up HPV test was negative or cervical abnormality had been effectively treated).
34. Seropositive for Trypanosoma cruzi or the Human T-lymphotropic virus type I or type II (HTLV-I/II) (testing required in endemic regions only)

35. Any other illness or infection (latent or active) that, in the Investigator's opinion, could have been exacerbated by either study medication

36. Any hepatic or renal function value grade 2 or higher at Screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome, unless, in the Investigator's opinion, the abnormality was due to a condition that had resolved (e.g., recent interferon treatment subsequently discontinued) and levels returned to WNL.

10.3 Appendix C

Summary of Safety from Phase 2 Studies of Campath

The original evidence of the efficacy and safety of alemtuzumab in B-CLL patients provided in support of its licensure was derived from 3, single-arm clinical studies in previously treated patients who had been exposed to prior therapies that included alkylating agents and fludarabine: two early Phase 2 studies 125-005-C92 and 125-009- C92, followed by a confirmatory Phase 2 study CAM211 (see Table 43). Study CAM211, was an international, multi-center study, designed as a pivotal trial to confirm the efficacy and safety of alemtuzumab in the heavily pre-treated B-CLL population evaluated in the pilot Phase 2 studies. Together, these Phase 2 studies defined a population of patients with an especially poor prognosis and who were unlikely to have an objective response to other available treatments.

Table 43: Overview of Clinical Trial Design for Phase 2 and Phase 3 Studies of Campath in CLL and B-CLL

	Phase 2			**Phase 3**
Study	**CAM211**	**125-005-C92**	**125-009-C92**	**CAM307**
N	**93**	**40**	**24**	**297**
Primary Diagnosis	B-CLL patients who had received an alkylating agent and had failed fludarabine	CLL patients who failed to respond or relapsed with first-line therapy or subsequent chemotherapy	CLL patients who failed to respond to or relapsed following treatment with fludarabine	B-CLL patients who had not received prior treatment
Design	Open-label, single arm	Open-label, single arm	Open-label, single arm	Open-label, randomized, active controlled
Comparator	None	None	None	Chlorambucil
Number of prior treatment regimens med (range)	3 (2-7)	3 (1-10)	3 (1-8)	N/A
Campath dose	30 mg IV 3 times/week	30 mg IV (or SC) 3 times/week	30 mg IV 3 times/week	30 mg IV 3 times/week
Duration of infusion	2 hours	2 hours: could be reduced to 30 minutes	2 hours: could be reduced to 30 minutes	2 hours

Table 43: Overview of Clinical Trial Design for Phase 2 and Phase 3 Studies of Campath in CLL and B-CLL

	Phase 2			Phase 3
Study	**CAM211**	**125-005-C92**	**125-009-C92**	**CAM307**
N	**93**	**40**	**24**	**297**
Duration of treatment	Tied to response; maximum of 12 weeks	12 weeks	16 weeks	Maximum of 12 weeks
Premedications	50 mg diphenhydramine; 650 mg acetaminophen	1 g paracetamol; 200 mg hydrocortisone IV or 10 mg chlorpheniramine IV	Optional	50 mg IV diphenhydramine; 500-1000 mg acetaminophen or paracetamol
Prophylactic antibiotics	TMP/SMXa DSa and famciclovir from Day 8 to at least 2 months post-treatment	Optional	Optional	TMP/SMXa DSa and famciclovir while on therapy and for at least 2 months post-treatment or until CD4 ≥ 200 /μL

[a]Trimethoprim/Sulfamethoxasole (TMP/SMX) Double Strength (DS)

The safety database for Campath submitted in the original BLA filing for Campath consisted of 157 patients from the Phase 2 studies in whom treatment was administered at 30 mg 3 times per week for 12 to 16 weeks. Based on the experience in the early Phase 2 studies 125-005-C92 and 125-009-C92, the pivotal study CAM211 included protocol-required prophylactic medication to reduce the frequency and/or intensity of infusion-associated reactions (IARs) and infections.

The most frequently reported adverse events (>10% of patients) in the Phase 2 experience were infusion-related reactions, including fever, rigors, nausea, vomiting, hypotension, rash urticarial, and dyspnea. While most events were grade 1 or 2 in severity, the incidence of severe events (Grade 3 or 4) was relatively frequent in the Phase 2 population (fever, 17%; rigors, 15%; hypotension, 5%; vomiting, 4%; nausea, 2%; and hypotension).

Overall, 85 patients (54.1%) experienced at least 1 serious adverse event (SAE); in 68 patients (43.3%) at least 1 serious event was grade 3 or 4 in severity. Serious adverse events were most commonly associated with infection or hematologic toxicities. SAEs reported in >5% of patients included fever, pneumonia, sepsis, dyspnea, granulocytopenia, thrombocytopenia, and CMV infection.

A total of 17 (10.8%) of the 157 B-CLL patients died during the treatment period or within 30 days of the last dose of Campath. The causes of death included infections in 8 patients including pneumonia (5), sepsis (2), and rhinocerebral mucormycosis (1); B- CLL disease progression in 5 patients; and pulmonary embolism, hemoptysis secondary to pre-existing thrombocytopenia, cerebral haemorrhage, and suicide in 1 patient each.

Overall, 93 (59.2%) of the 157 previously-treated B-CLL patients experienced at least one infection. Grade 3 or 4 infections were reported in 43 patients (27.4%). Frequent infections (>10% of patients) included pneumonia and blood borne infections (the majority were related to indwelling central catheters); some were opportunistic infections (P. jiroveci pneumonia and aspergillus pneumonia). Other opportunistic infections included CMV, herpes zoster rhinocerebral mucormycosis, listeria meningitis and PML.

Overall, opportunistic infections occurred in 12.7% of patients on study and in decreased in incidence during the post-study period in this heavily pre-treated population of patients already at high risk for the development of opportunistic infections.

Cytopenias were common during study and not unexpected given the underlying hematologic malignancy in the patient population. At baseline, 42 patients (26.8%) had grade 3 or 4 thrombocytopenia. Thrombocytopenia was common during the treatment period, although rapid recovery was noted at study end and 2 months post-treatment. Eight (5.1%) of the 157 patients had bleeding events that were serious in nature. One patient treated with Campath in CAM211 developed ITP 3 weeks after the end of treatment. Despite a variety of treatments administered, including splenectomy, the patient died of an intra-abdominal haemorrhage 39 days post-treatment.

Neutropenia developed or worsened from baseline in many patients beginning within the first 2 weeks of treatment and peaking during weeks 5 to 8. The neutropenia resolved in the majority of patients by the 2-month follow-up. Pancytopenia was reported in 8 (5.1%) of the 157 patients; in 5 patients the event was considered to be grade 3 or 4 in severity or serious in nature. The reported cases of pancytopenia resolved within 2 weeks in all cases, either after an interruption in therapy or following the end of treatment.

Summary of Safety from Phase 3 Study of Campath in B-CLL (CAM307)

The promising Phase 2 data prompted a Phase 3 clinical trial using Campath at an earlier stage of the disease. In the Phase 3 study CAM307, patients were randomized to a target dosing regimen of Campath (N=147) 30 mg/day IV administered 3 times per week for up to 12 weeks or a

dosing regimen of chlorambucil (N=147) 40 mg/m^2 PO once every 28 days. Among all patients in the Campath arm, the AEs experienced in ≥ 10% of patients were pyrexia, CMV viremia, chills, nausea, hypotension, CMV infection, urticaria, headache, dyspnea, hypertension, rash, fatigue, vomiting, diarrhea, insomnia, and neutropenia. Many of the events were IARs which occurred during the first week of infusions, were mild or moderate in severity, and generally decreased in frequency with subsequent doses. Premedication with diphenhydramine and acetaminophen appeared to be helpful in reducing the incidence and severity of subsequent IARs.

The overall incidence of on-treatment SAEs for the Campath arm was 35.4%. The most frequently reported SAE was CMV viremia. SAEs experienced in >5% of patients were CMV viremia, pneumonia, pyrexia, and CMV infection.

During treatment or within 30 days of the last dose of study drug there was 1 death in the Campath arm; the cause of death was infection (Candida albicans sepsis) and kidney, heart and lung insufficiency, and was assessed as not related to study drug.

Among the patients in the Campath arm, the infections experienced in >10% of patients were CMV viremia, and CMV infection.

With the exception of 1 patient who experienced pure red cell aplasia 6 months after completing treatment with Campath, there were no reports of pancytopenia or bone marrow aplasia in CAM307. In Study CAM307 12.2% of patients treated with Campath had 1 or more episodes of new onset CTCAE grade 3 or 4 thrombocytopenia during the on-treatment period. Forty-one percent (41.1%) of patients treated with Campath had 1 or more episodes of new onset CTCAE grade 3 or 4 neutropenia during the on-treatment period.

One patient experienced an event of hemolytic anemia (one in each arm) and 1 patient experienced autoimmune hemolytic anemia (in the chlorambucil arm).

Summary of Clinical Experience with Campath

The Phase 2 clinical studies included patients with long-standing B-CLL with a history of intensive prior therapy, whereas the Phase 3 population had not been previously treated for B-CLL. In general, IARs were common, many of which were severe in nature and occurred in association with the first few infusions. Although hematologic toxicity was common, recovery was seen during the study or shortly thereafter in most patients. Infections were also common,

some being grade 3 and 4 in intensity and opportunistic in nature, although the incidence of such infections appeared to improve with prophylaxis.

Postmarketing Experience with Campath

Since approval on 07 May 2001, the safety of Campath has been continuously monitored through vigilant postmarketing surveillance. Postmarketing safety information received by Genzyme Corporation through 07 May 2012 (the data cut-off date for annual safety reporting) is summarized below.

The adverse event cases in the Genzyme safety database included in this summary are from sources including but not limited to spontaneous postmarketing reports, investigator-sponsored studies, studies or case presentation in literature, and regulator-reported cases. These events are reported voluntarily from a population of uncertain size, may have incomplete or missing information, and follow up information may not be available; therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In the postmarketing setting, an estimated number of 41,720 patients were treated with Campath as of 07 May 2012. This number is based on worldwide sales and the assumption that each patient is treated for B-CLL and therefore, receives 3 vials per week and an average of 8 weeks of treatment. The estimated number of patients treated does not include the patients treated in Genzyme-sponsored clinical trials in MS or B-CLL.

The safety data has been identified during post approval use of Campath for the treatment of B-CLL, as well as for the treatment of other disorders including use in malignancies other than CLL, solid organ transplantation, hematologic stem cell transplant, multiple sclerosis and other autoimmune disorders.

The dose used for these other conditions is diverse and wide-ranging. In solid organ transplant the use is mainly as induction therapy; for renal transplant, as part of regimens with immunosuppressants, the dose starts at 20mg IV on two consecutive days (Watson, 2005, *Am J Tranplant*) or when used alone as a single IV dose of 30mg (Hanaway, 2011, *NEJM*); similar doses are used for lung transplant (Shyu, 2011, *J Heart Lung Transplant*), kidney-pancreas and pancreatic transplant (Muthusamy, 2008, *Am J Transplant*), among other isolated or multivisceral allografting procedures on which use has been reported. The use in hematologic stem cell transplant has been for reduce intensity conditioning including doses of 10 mg per day from days -5 to -1 (Faulkner, 2004, *Blood*) and 20 mg per day from days -8 to -4 (Ho, 2004, *Blood*), among others. The use in oncology beyond the approved indication, has been

mainly on T-cell lymphoproliferative conditions at doses similar to the approved posology (Boyd, 2008, *Expert Rev Anticancer Ther*). Finally, use in other autoimmune conditions including Rheumatoid Arthritis and different types of vasculitides has been reported, stemming from the early observations of the University of Cambridge research group.

Overall, the events described below encompass the observations across the different populations and diseases on which the medication has been used.

In the postmarketing setting, an estimated number of 41,720 patients were treated with Campath as of 07 May 2012. This number is based on worldwide sales and the assumption that each patient receives 3 vials per week and an average of 8 weeks of treatment.

In postmarketing surveillance, serious and sometimes fatal infusion reactions including bronchospasm, hypoxia, syncope, pulmonary infiltrates, Acute Respiratory Distress Syndrome (ARDS), respiratory arrest, myocardial infarction, arrhythmias, acute cardiac insufficiency and cardiac arrest have been observed following Campath treatment for B-CLL. These events are captured in the prescribing information for Campath.

Hematologic adverse events, including lymphopenia (stemming from the primary mechanism of action), neutropenia, thrombocytopenia, and anemia are commonly associated with use of Campath. Severe, prolonged, and in rare instances fatal myelosuppression has occurred in patients with leukemia and lymphoma receiving Campath. While lymphopenia is an expected pharmacologic effect of Campath, neutropenia, thrombocytopenia, and anemia are likely due primarily to underlying bone marrow disease, residual bone marrow toxicity from prior therapy, and effects of concurrent treatments for B-CLL.

There have been uncommon (<1%) reports of Immune Thrombocytopenia (ITP) from the postmarketing setting in patients treated with Campath for malignancy, transplant, immunosuppressive therapy, graft versus host disease (GvHD) and MS. In 8% of these cases the patient (treated for either B-CLL or prophylaxis against) experienced a fatal outcome. There were no fatal cases reported from off-label use in MS.

The reported baseline incidence of ITP in patients with hematological malignancies is approximately 2% (Cheson, 2001, *Cancer: Principles and Practice of Oncology*; Diehl, 1998, *Semin Oncol*); the number of reports of ITP in the Campath treated population does not appear to be higher than baseline.

There have been uncommon (<1%) reports of pancytopenia received in patients treated with Campath.

Rare (<0.1%) reports of thyroid disorders have been received in patients who were treated with Campath for malignancy, transplant and demyelinating disorders. The number of reported events of hyperthyroidism and hypothyroidism were similar.

Very rare (<0.01%) reports of anti-GBM disease have been received from off-label use with Campath treatment for MS and vasculitis. Anti-GBM disease has not been reported in the post marketing setting when used in B-CLL.

In postmarketing surveillance, serious and sometimes fatal viral, bacterial, protozoan and fungal infections, including those due to reactivation of latent infections, have been observed. Fatal infections have been reported in patients who received Campath in the postmarketing setting for GvHD, malignancy, vasculitis, transplant, lymphoproliferative disorder, and progressive MS. In patients receiving Campath, the most frequent causes of fatal infection were sepsis/septic shock, pneumonia, CMV, aspergillus infections, and Epstein-Barr virus associated disease (viremia and EBV associated lymphoproliferative disorder). A total of 8 fatal infections occurred in patients with progressive MS who died of pneumonia or urosepsis 6 to 13 years after first receiving Campath.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the John Cunningham virus (JCV) which latently infects the vast majority of the adult population. It is usually associated with conditions causing profound immunodeficiency, classically seen in patients with human immunodeficiency virus/acquired immune deficiency syndrome. PML is known to be associated with some immunosuppressive therapies. In addition, PML has also been associated with various lymphoproliferative malignancies, including B-CLL. B-CLL can increase a patient's risk for developing PML due to immunodeficiency (Gonzalez, 1999, *Hematol Cell Ther*; Ooi, 2009, *International Journal of General Medicine*). Rare (<0.1%) cases of PML have been reported in patients treated with Campath. No cases of PML have been reported from off-label use in MS patients. In the majority of PML cases, the patients had B-CLL. The remaining cases occurred in a patient who received Campath for transplant. The frequency of spontaneous reporting of PML in patients treated with Campath has occurred at an average frequency of 0.05%. The reported background frequency of PML in patients with B-CLL is 0.07-0.5% (Power, 2000, *Neurology*; Morra, 1999,

Hematol Cell Ther; Bower, 1997, *Neurology*). Based on the available data, there is currently no evidence that Campath impacts the incidence of PML in patients with B-CLL.

The recommended dosing regimen for B-CLL patients involves gradual escalation to a maximum dose of 30 mg administered 3 times per week for up to 12 weeks (total dose >1,000 mg per the product prescribing information). In contrast, the intended recommended dosing regimen for alemtuzumab for use in MS is 2 treatment courses (one 5-day course and one 3-day course) of 12 mg/day, administered 12 months apart (total dose of 96 mg). MS patients are generally younger than B-CLL patients with fewer comorbidities, less immunoincompetence (as a result of prior treatment or disease itself), and less residual toxicity from prior therapies.

While IARs, infections, and cytopenias have been observed with use of alemtuzumab in MS (refer to Section 5.1.7) and B-CLL, events tend to be more severe, and in some cases more frequent, in the B-CLL population. Among the reported cases in the postmarketing setting, certain infections (e.g. CMV) are reported more often in the B-CLL indication and overall are more severe compared with reported events in the MS setting.

10.4 Appendix D

Incidence of Treatment-Emergent Adverse Events Experienced by at Least 10% of Patients in Any Treatment Group by MedDRA SOC and Preferred Term (Active-controlled experience)

	IFNB-1a	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled
	(N=496)	(N=919)	(N=269)	(N=1188)
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Event	470 (94.8)	897 (97.6)	266 (98.9)	1163 (97.9)
Gastrointestinal disorders	166 (33.5)	454 (49.4)	179 (66.5)	633 (53.3)
Nausea	51 (10.3)	200 (21.8)	93 (34.6)	293 (24.7)
Diarrhoea	29 (5.8)	108 (11.8)	50 (18.6)	158 (13.3)
Vomiting	21 (4.2)	97 (10.6)	44 (16.4)	141 (11.9)
Dyspepsia	25 (5.0)	80 (8.7)	32 (11.9)	112 (9.4)
General disorders and administration site conditions	318 (64.1)	602 (65.5)	201 (74.7)	803 (67.6)
Pyrexia	47 (9.5)	278 (30.3)	93 (34.6)	371 (31.2)
Fatigue	78 (15.7)	192 (20.9)	77 (28.6)	269 (22.6)
Chills	20 (4.0)	90 (9.8)	42 (15.6)	132 (11.1)
Chest discomfort	10 (2.0)	70 (7.6)	44 (16.4)	114 (9.6)
Pain	18 (3.6)	70 (7.6)	28 (10.4)	98 (8.2)
Influenza like illness	136 (27.4)	65 (7.1)	26 (9.7)	91 (7.7)
Injection site erythema	119 (24.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	267 (53.8)	658 (71.6)	205 (76.2)	863 (72.6)
Nasopharyngitis	84 (16.9)	216 (23.5)	73 (27.1)	289 (24.3)
Urinary tract infection	42 (8.5)	164 (17.8)	51 (19.0)	215 (18.1)
Upper respiratory tract infection	58 (11.7)	145 (15.8)	58 (21.6)	203 (17.1)
Sinusitis	36 (7.3)	101 (11.0)	32 (11.9)	133 (11.2)

	IFNB-1a	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled
	(N=496)	(N=919)	(N=269)	(N=1188)
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Bronchitis	16 (3.2)	65 (7.1)	27 (10.0)	92 (7.7)
Injury, poisoning and procedural complications	98 (19.8)	240 (26.1)	97 (36.1)	337 (28.4)
Contusion	29 (5.8)	92 (10.0)	45 (16.7)	137 (11.5)
Musculoskeletal and connective tissue disorders	197 (39.7)	434 (47.2)	153 (56.9)	587 (49.4)
Pain in extremity	49 (9.9)	123 (13.4)	55 (20.4)	178 (15.0)
Arthralgia	45 (9.1)	116 (12.6)	36 (13.4)	152 (12.8)
Back pain	41 (8.3)	114 (12.4)	49 (18.2)	163 (13.7)
Muscular weakness	54 (10.9)	71 (7.7)	30 (11.2)	101 (8.5)
Muscle spasms	31 (6.3)	64 (7.0)	30 (11.2)	94 (7.9)
Myalgia	28 (5.6)	62 (6.7)	36 (13.4)	98 (8.2)
Nervous system disorders	344 (69.4)	675 (73.4)	223 (82.9)	898 (75.6)
Headache	114 (23.0)	487 (53.0)	184 (68.4)	671 (56.5)
Multiple sclerosis relapse	216 (43.5)	250 (27.2)	70 (26.0)	320 (26.9)
Paraesthesia	51 (10.3)	118 (12.8)	35 (13.0)	153 (12.9)
Dizziness	30 (6.0)	92 (10.0)	52 (19.3)	144 (12.1)
Hypoaesthesia	58 (11.7)	91 (9.9)	39 (14.5)	130 (10.9)
Dysgeusia	49 (9.9)	86 (9.4)	33 (12.3)	119 (10.0)
Psychiatric disorders	154 (31.0)	288 (31.3)	116 (43.1)	404 (34.0)
Insomnia	75 (15.1)	160 (17.4)	57 (21.2)	217 (18.3)
Depression	57 (11.5)	72 (7.8)	34 (12.6)	106 (8.9)
Anxiety	34 (6.9)	65 (7.1)	33 (12.3)	98 (8.2)
Respiratory, thoracic and mediastinal disorders	94 (19.0)	356 (38.7)	136 (50.6)	492 (41.4)
Oropharyngeal pain	24 (4.8)	104 (11.3)	35 (13.0)	139 (11.7)

	IFNB-1a	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled
	(N=496)	(N=919)	(N=269)	(N=1188)
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dyspnoea	8 (1.6)	86 (9.4)	43 (16.0)	129 (10.9)
Cough	20 (4.0)	84 (9.1)	33 (12.3)	117 (9.8)
Skin and subcutaneous tissue disorders	130 (26.2)	716 (77.9)	252 (93.7)	968 (81.5)
Rash	27 (5.4)	445 (48.4)	176 (65.4)	621 (52.3)
Urticaria	9 (1.8)	157 (17.1)	80 (29.7)	237 (19.9)
Pruritus	12 (2.4)	152 (16.5)	63 (23.4)	215 (18.1)

Note: MedDRA version 13.1 was used for coding.
Note: Percentages are based on the number of treated patients in the corresponding treatment group.
Note: A patient is counted only once within each SOC/PT.
Note: SOCs are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

10.5 Appendix E

Experience with 24 mg Dose

As described in Section 4, alemtuzumab 12 mg/day (given in 2 cycles) is efficacious in patients with RRMS and is associated with statistically significant improvements in relapse, disability, and MRI endpoints compared with Rebif. Across all 3 active-controlled studies (CAMMS324, CAMMS323, and CAMMS223), alemtuzumab 12 mg/day significantly reduced the relapse rate, a primary endpoint, compared with Rebif and a significantly higher percentage of patients treated with alemtuzumab 12 mg/day were relapse free compared with the Rebif treated patients (Section 3.2.1). Alemtuzumab 12 mg/day also significantly reduced the risk of SAD (a primary endpoint) and improved EDSS scores compared with Rebif in 2 of the 3 studies (Section 3.2.2). In addition, alemtuzumab 12 mg/day reduced the risk of developing new or enlarging T2-hyperintense lesions, Gd-enhancing lesions, or new T1-hypointense lesions, and significantly reduced the rate of brain atrophy compared with Rebif (Section 3.2.3).

In addition to the 12 mg/day dosing regimen, a 24 mg/day regimen was evaluated in studies CAMMS324 and CAMMS223. Overall, exploratory analyses found few statistically significant differences between the 2 dose levels on clinical efficacy endpoints. In particular, efficacy was comparable for the co-primary endpoints in both studies. However, there were some notable (though usually statistically non-significant) differences in efficacy between the dose levels. In CAMMS324, the 12 mg/day dosing regimen showed less efficacy than 24 mg/day on most MRI-related endpoints, including the secondary endpoint of T2-hyperintense lesion volume change from baseline (p=0.0057 at Month 24), new or enlarging T2-hyperintense lesion activity (p=0.0396 at Month 24, though not significant overall), Gd-enhancing lesion activity (overall p=0.0841), and T1-hypointense lesion activity (p=0.0192). Since the MRI endpoints are a more sensitive measure of disease activity than clinical endpoints (Martinelli Boneschi, 2004, *Mult Scler*), the consistently smaller effect on MRI outcomes with the 12 mg/day dose compared with 24 mg/day suggests there could be a further waning of efficacy, with potential impact on clinical outcomes, at doses below 12 mg/day.

In the Phase 2 study CAMMS223, the 2 doses showed generally comparable efficacy, but there were non- statistically significant differences in favor of the 24 mg/day dose over the 12 mg/day dose in most clinical endpoints (i.e., relapse reduction, EDSS change from baseline, and MSFC), and on reduction in brain atrophy. The 12 mg/day dose appeared (non-significantly) better only on 6- month SAD (though 24 mg/day was better on 3-month SAD) and T2 lesion volume change.

Consistent with the efficacy observations, no apparent differences were noted between the 24 mg/day and 12 mg/day dose levels in the pharmacodynamic response as measured in peripheral blood, despite the expectedly higher serum concentrations of alemtuzumab observed after administration of the higher dose. The longitudinal pattern of lymphocyte depletion and repopulation was similar for the 24 mg/day and 12 mg/day doses in the CAMMS324 (Section 6.1.1.2) and CAMMS223 studies.

Based upon pooled safety data from all studies, the types of AEs reported in patients receiving the 24 mg/day dose were generally comparable to those reported in patients receiving alemtuzumab 12 mg/day, although the overall frequency of events was often higher in the 24 mg/day group. Few apparent dose-related trends were seen.

Overview of Adverse Events in the 3-Year Active Controlled Experience (Pool E)

AEs, n (%)	IFNB-1a (N=496)	Alemtuzumab 12 mg (N=919)	Alemtuzumab 24 mg (N=269)	Alemtuzumab 12 mg + 24 mg (N=1188)
All events	470 (94.8)	897 (97.6)	251 (98.9)	1163 (97.9)
Grade 1	401 (80.8)	817 (88.9)	251 (93.3)	1068 (89.9)
Grade 2	405 (81.7)	840 (91.4)	259 (96.3)	1099 (92.5)
Grade 3	110 (22.2)	232 (25.2)	96 (35.7)	328 (27.6)
Grade 4	10 (2.0)	27 (2.9)	15 (5.6)	42 (3.5)
Serious AEs	96 (19.4)	177 (19.3)	51 (19.0)	228 (19.2)
Deaths	1[a]	4 (0.4)	1 (0.4)	5 (0.4)
AEs leading to treatment discontinuation	39 (7.9)	22 (2.4)	7 (2.6)	29 (2.4)
AEs leading to study discontinuation	21 (4.2)	3 (0.3)	1 (0.4)	4 (0.3)

[a]This death in a patient treated with IFNB-1a occurred during the extension period of Phase 2 Study CAMMS223

Therefore, the lowest efficacious and safe dose (12 mg/day) is the recommended dose for the treatment of relapsing forms of MS.